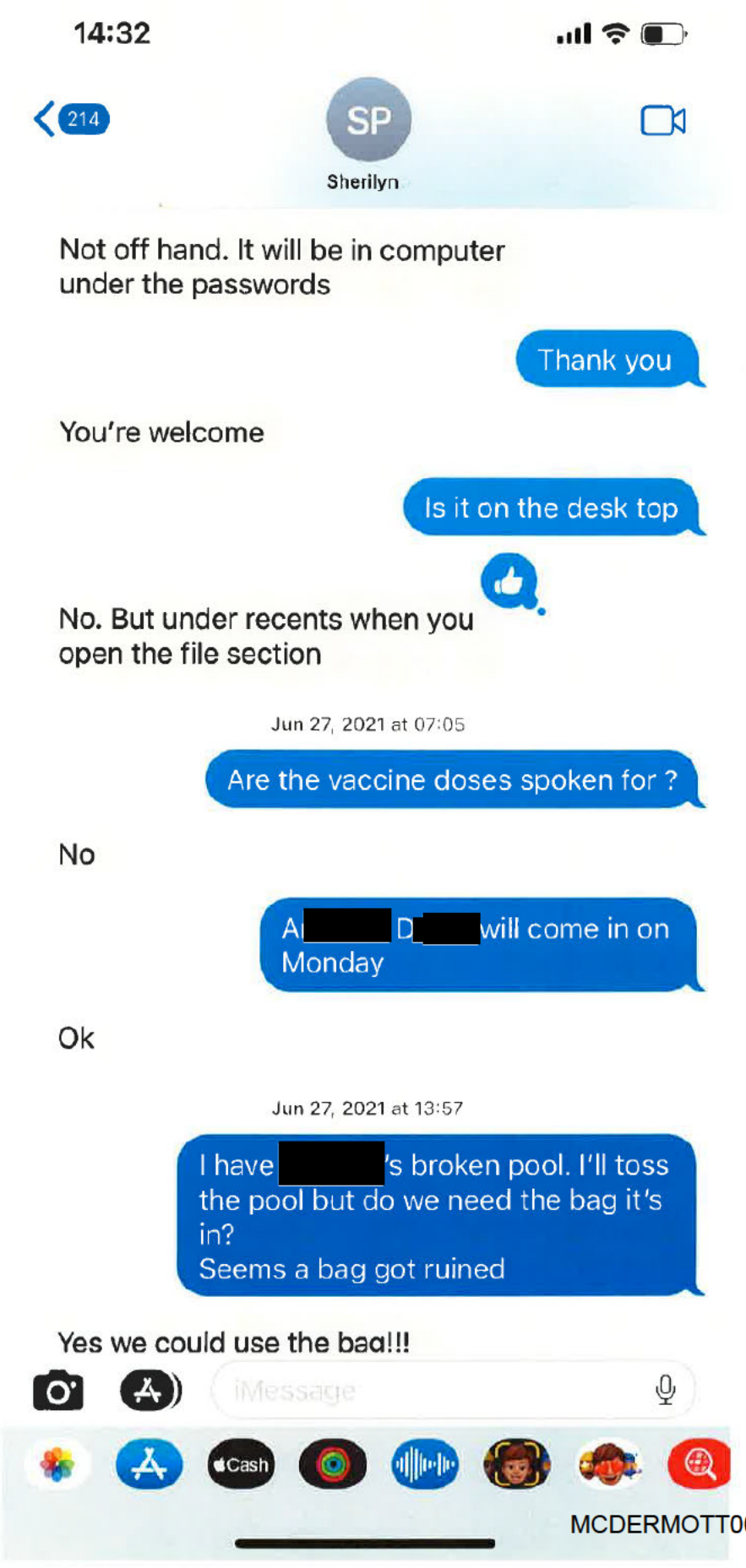
Exhibit A


7:07
84%
Kelly Mcdermott
Are we giving to men, too?
Yeah
Yay! 🎉
Let people know?
H[redacted] S[redacted]
And her husband
Can you schedule to administer to your people and document
Yes
Will probably d to be later in the dsy
Text message

Exhibit B



MCDERMOTT00005095

Exhibit C

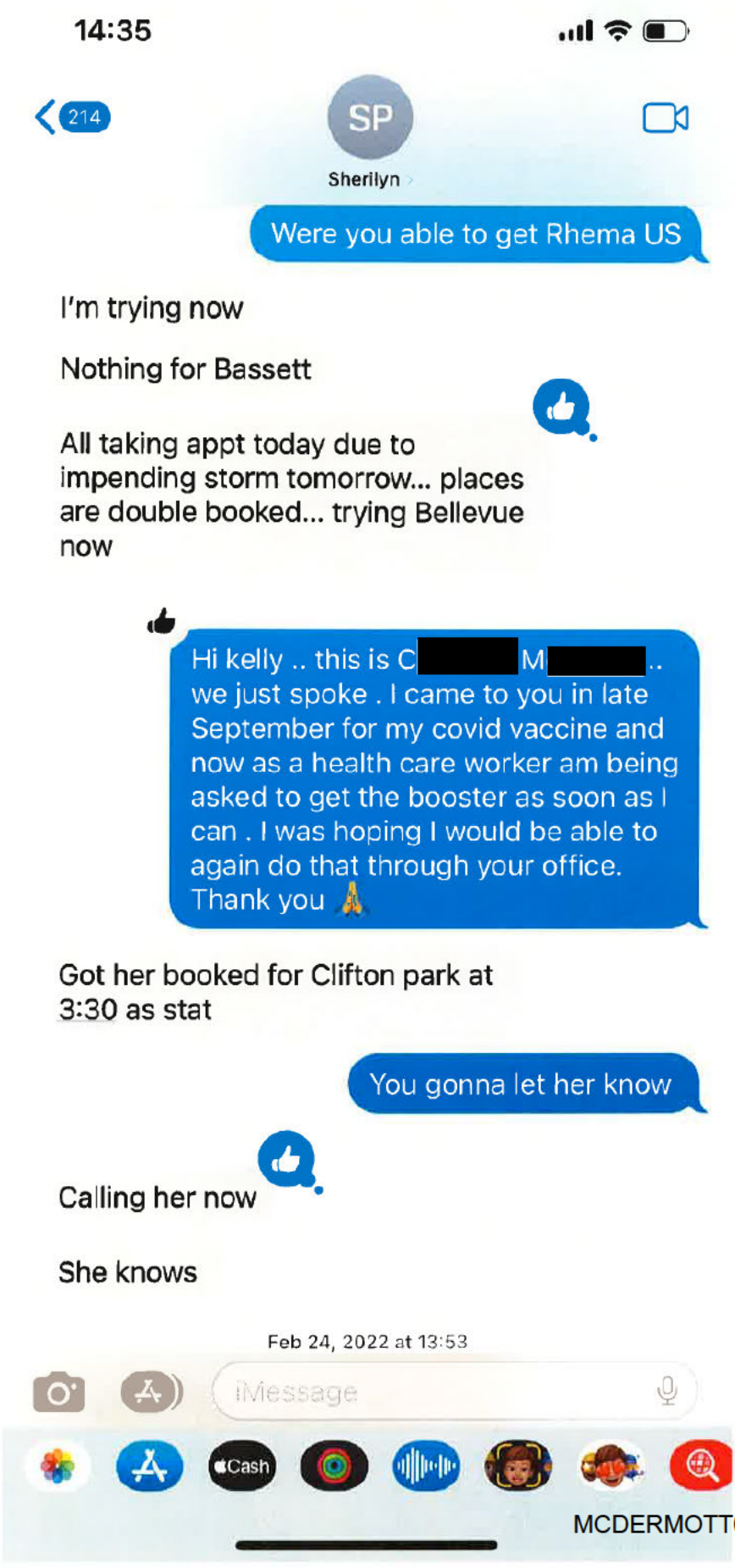


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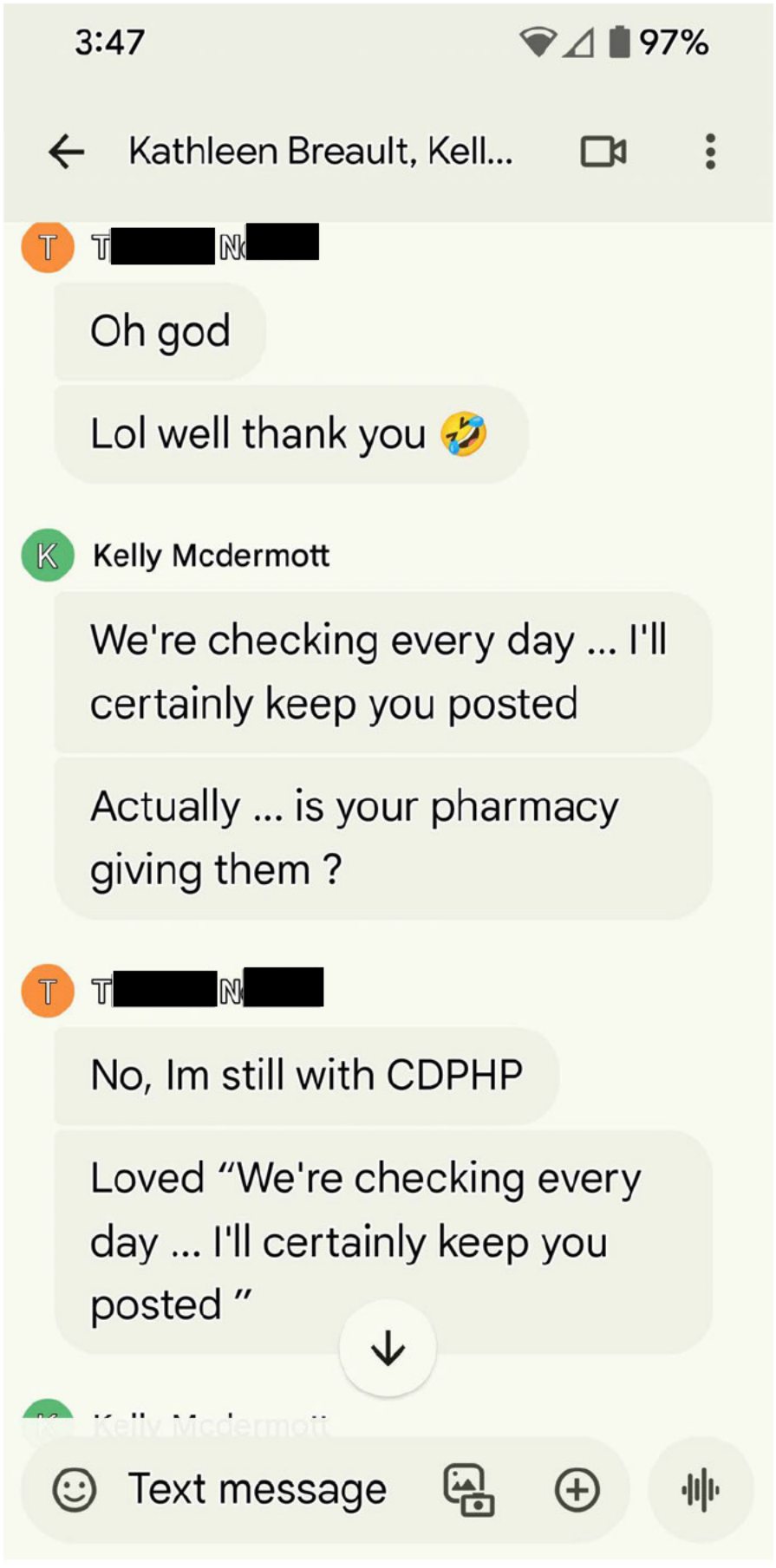
Exhibit D


3:47
97%
Kathleen Breault, Kell...
T [redacted] N [redacted]
Oh god
Lol well thank you 🤣
K Kelly Mcdermott
We're checking every day ... I'll certainly keep you posted
Actually ... is your pharmacy giving them ?
T [redacted] N [redacted]
No, Im still with CDPHP
Loved “We're checking every day ... I'll certainly keep you posted ”
Text message

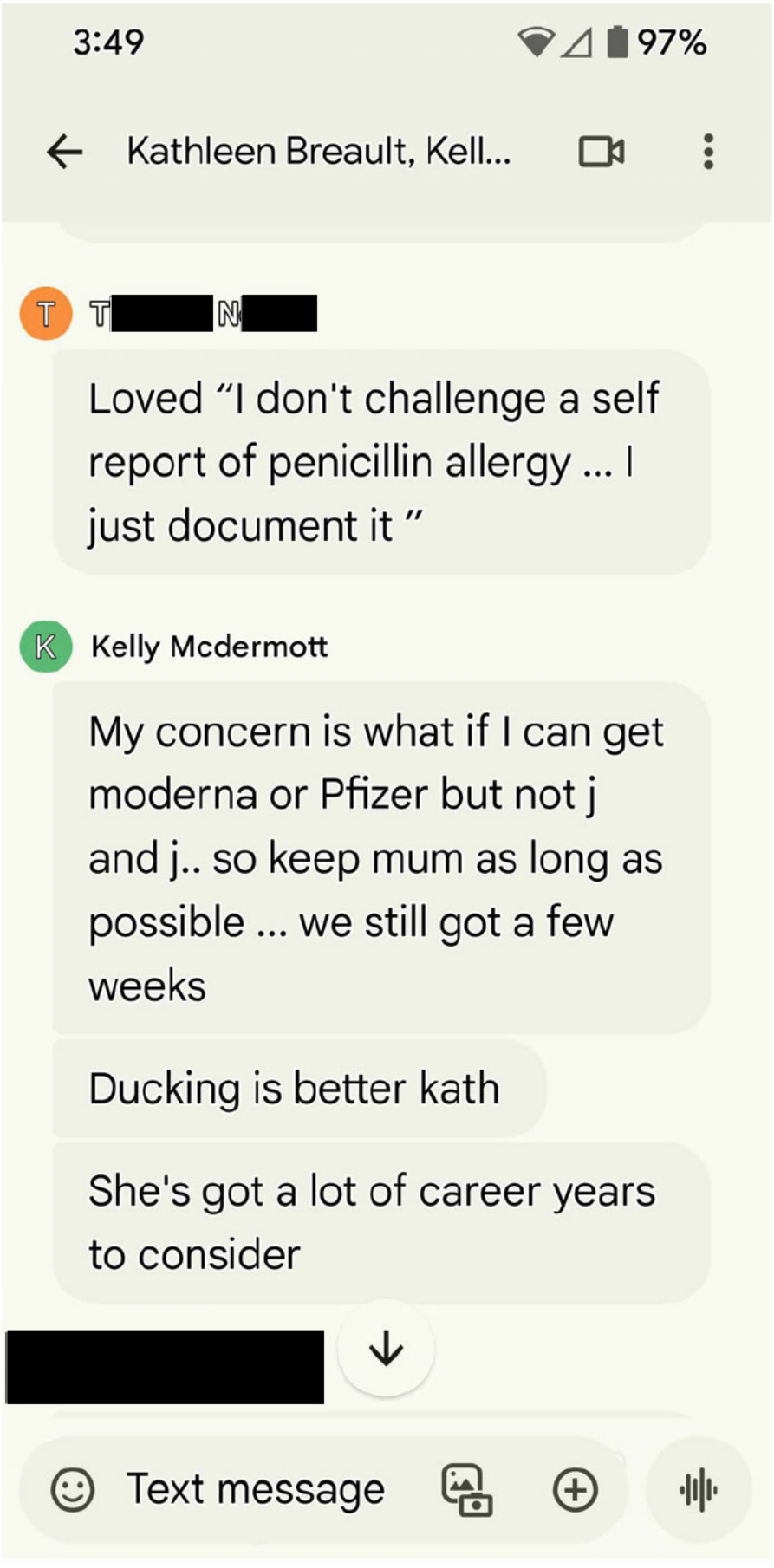

3:49
97%
Kathleen Breault, Kell...
T [redacted] N [redacted]
Loved “I don't challenge a self report of penicillin allergy ... I just document it ”
Kelly Mcdermott
My concern is what if I can get moderna or Pfizer but not j and j.. so keep mum as long as possible ... we still got a few weeks
Ducking is better kath
She's got a lot of career years to consider
[redacted]
Text message

Exhibit E

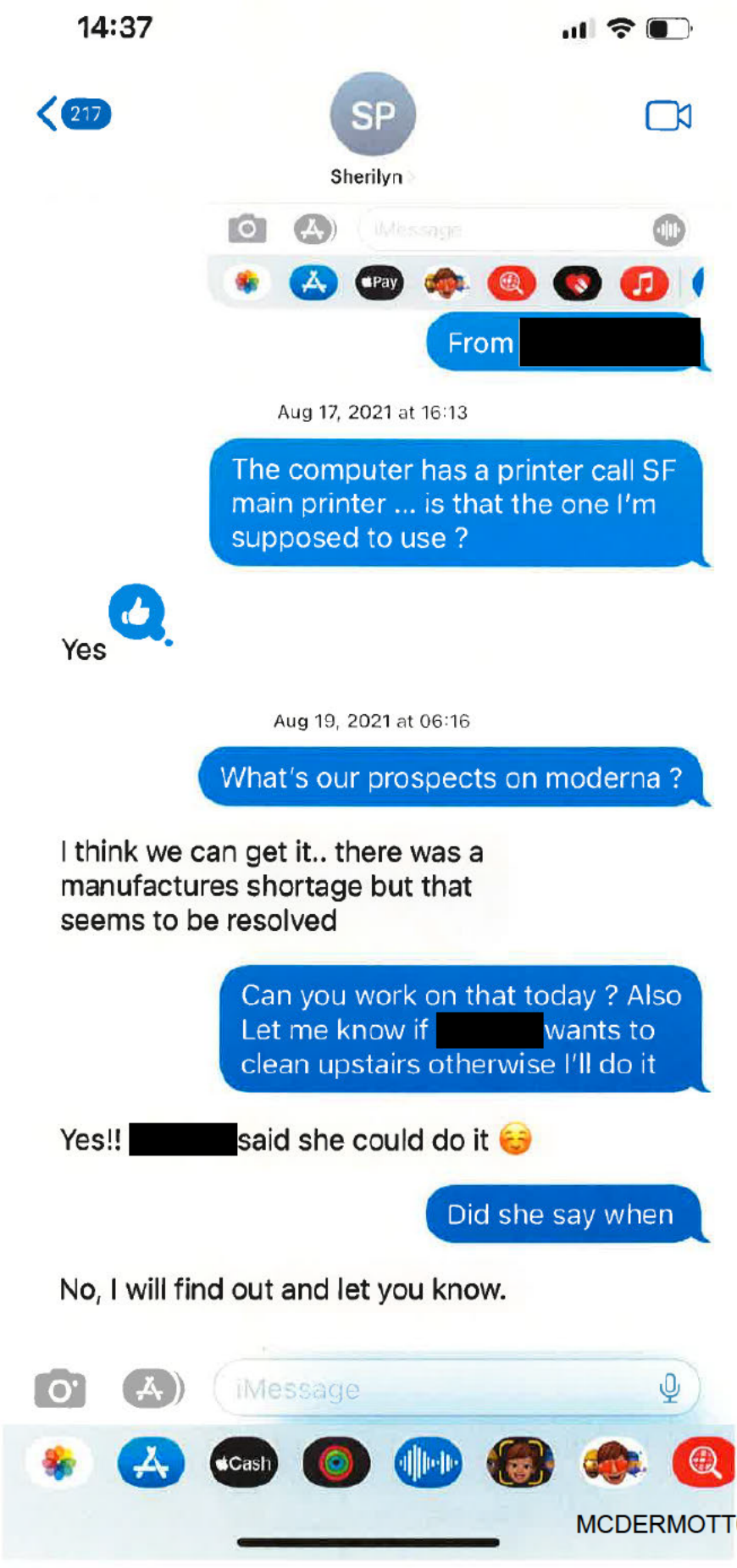


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Exhibit F

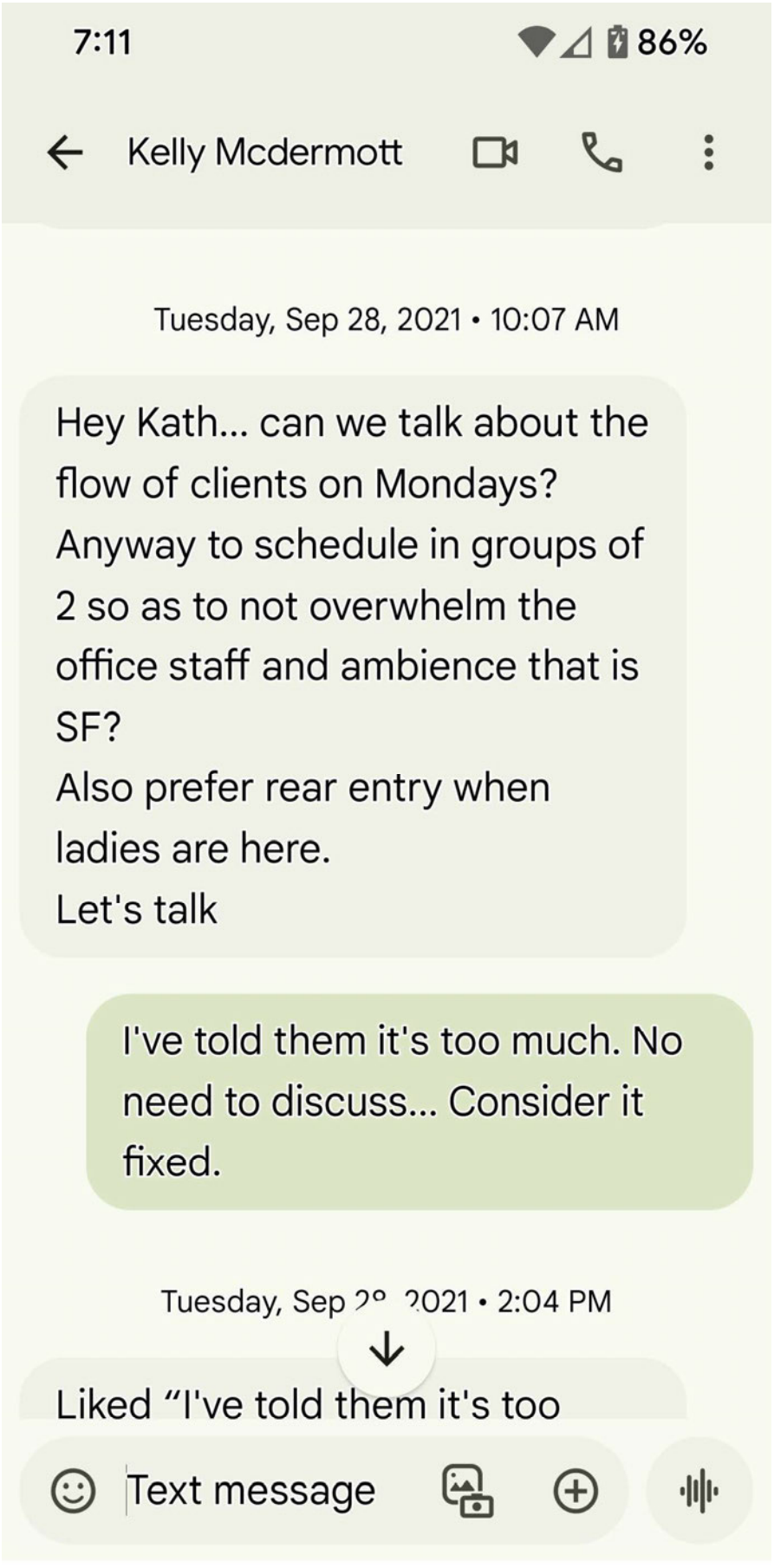
7:11
86%
Kelly Mcdermott
Tuesday, Sep 28, 2021 • 10:07 AM
Hey Kath... can we talk about the flow of clients on Mondays? Anyway to schedule in groups of 2 so as to not overwhelm the office staff and ambience that is SF?
Also prefer rear entry when ladies are here.
Let's talk
I've told them it's too much. No need to discuss... Consider it fixed.
Tuesday, Sep 2? 2021 • 2:04 PM
Liked "I've told them it's too
Text message

Exhibit G

communications medicine

ARTICLE

https://doi.org/10.1038/s43856-022-00075-x OPEN

Modelling the impact of vaccine hesitancy in prolonging the need for Non-Pharmaceutical Interventions to control the COVID-19 pandemic

Daniela Olivera Mesa[1✉], Alexandra B. Hogan[1], Oliver J. Watson[1], Giovanni D. Charles[1], Katharina Hauck[1], Azra C. Ghani[1] & Peter Winskill[1]

Abstract

Background Vaccine hesitancy – a delay in acceptance or refusal of vaccines despite availability – has the potential to threaten the successful roll-out of SARS-CoV-2 vaccines globally. In this study, we aim to understand the likely impact of vaccine hesitancy on the control of the COVID-19 pandemic.

Methods We modelled the potential impact of vaccine hesitancy on the control of the pandemic and the relaxation of non-pharmaceutical interventions (NPIs) by combining an epidemiological model of SARS-CoV-2 transmission with data on vaccine hesitancy from population surveys.

Results Our simulations suggest that the mortality over a 2-year period could be up to 7.6 times higher in countries with high vaccine hesitancy compared to an ideal vaccination uptake if NPIs are relaxed. Alternatively, high vaccine hesitancy could prolong the need for NPIs to remain in place.

Conclusions While vaccination is an individual choice, vaccine-hesitant individuals have a substantial impact on the pandemic trajectory, which may challenge current efforts to control COVID-19. In order to prevent such outcomes, addressing vaccine hesitancy with behavioural interventions is an important priority in the control of the COVID-19 pandemic.

Plain language summary

People refusing or delaying COVID-19 vaccination might impact current efforts to control the pandemic caused by SARS-CoV-2. Here, we have examined the effects of low vaccine uptake due to vaccine hesitancy on the need to prolong other public health measures to control the pandemic. We used mathematical modelling and data on vaccine hesitancy from population surveys across different countries. Our results suggest that when there is vaccine hesitancy and relaxation of other public health measures, mortality could increase by up to seven times compared with ideal vaccination coverage of the population. Furthermore, for some scenarios analysed, longer and more stringent public health measures would be required to compensate for lower vaccine uptake. Our work demonstrates that vaccine hesitancy might have a substantial health impact on the population, and therefore, it is a public health priority to increase trust in vaccines.

[1] MRC Centre for Global Infectious Disease Analysis; and the Jameel Institute, School of Public Health, Imperial College London, London, UK.
✉email: d.olivera-mesa17@imperial.ac.uk

The COVID-19 pandemic has simultaneously resulted in high global mortality and major economic disruptions. As a control measure, non-pharmaceutical interventions (NPIs) such as social distancing and mobility restrictions have been put in place worldwide and have successfully reduced transmission of the virus. However, these interventions are unsustainable in the long-term[1] and current hopes to control the pandemic rely heavily on vaccination.

In December 2020, the first vaccine against SARS-CoV-2 was approved; by May 2021, 14 vaccines had been licensed (https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/) and more than 1.3 billion vaccination doses administered worldwide (https://ourworldindata.org/covid-vaccinations#). Their reported efficacy against symptomatic disease ranges from 50% to over 95%[2–6]. Given the high basic reproduction number for SARS-CoV-2 (estimates range between 3–4)[1] high levels of vaccine uptake will be required to achieve herd immunity[7], particularly if children are not vaccinated during the first phase of roll-out.

One major concern that threatens to limit the impact of vaccination is vaccine hesitancy[8]. Population surveys have found that between 14%[9] and 27%[10] of adults say that they will not accept a vaccine if available, whilst between 14%[9] and 19%[10] say that they are uncertain. There is a large variation in vaccine hesitancy between countries, with the proportion saying that they would get a SARS-Cov-2 vaccine if it became available, ranging from 40% for France[10] to 89% for China[9]. In many countries, vaccine hesitancy is heterogenous across sub-populations depending on gender, age, ethnicity, religion, or socioeconomic status[9–11]. Surveys have highlighted the key drivers of SARS-CoV-2 vaccine hesitancy are related to concerns about the accelerated pace of vaccine development[11], side-effects[10] and the spread of misinformation about the pandemic[8]. Underlying reasons of vaccine hesitancy are a complex interaction between trust in government and health authorities[9] coupled with new information —and misinformation— on the vaccine safety and disease risk arising everyday[12].

In the present study, we aim to understand the likely impact of vaccine hesitancy on future control of the pandemic, using a mathematical model of SARS-CoV-2 transmission[7] to explore vaccine hesitancy through its impact on population coverage. We capture the effect of reduced coverage using measured levels of vaccine hesitancy from behavioural survey data[10] on self-reported intention to be vaccinated. Survey results are disaggregated by age and translated to vaccination coverage ranges per age group. Pandemic trajectories with low vaccination coverage due to vaccine hesitancy are compared to an ideal counterfactual assuming no vaccine hesitancy, in which we assume that a small proportion (5%) of the population cannot be reached for vaccination. This value is based on maximum vaccination uptake reported for England's current COVID-19 vaccine rollout (https://www.england.nhs.uk/statistics/statistical-work-areas/covid-19-vaccinations/). We model each scenario with both a high and a moderate vaccine efficacy profile that represents the range of efficacies of currently approved vaccines. Informed by current vaccine roll-out in high-income countries, we assume that vaccination started in January 2021 and is implemented at a rate that results in a total campaign of 10 months to fully vaccinate the population above 15 years old.

Our simulations suggest that mortality could be higher in countries with high vaccine hesitancy compared to an ideal vaccination and this could prolong the need for NPIs to remain in place. We show that to reduce this impact, vaccination campaigns could include less vulnerable groups, like children. Vaccine hesitancy is an important public health priority that needs to be addressed in order to control the current pandemic.

Methods

Vaccine hesitancy data. Attitudes towards COVID-19 vaccination were obtained from the Imperial College London YouGov Covid 19 Behaviour Tracker Data[10]. This data set includes weekly surveys about people's behaviours in response to COVID-19 (including vaccines) as well as standard demographic questions on age, gender and household structure. Ethics approval and informed consent were not required given that all data was publicly available and de-identified.

We extracted the survey results from 8th to 15th February 2021 for 10 European countries. To assess vaccine hesitancy, we used data from one question pertaining to COVID-19 vaccine acceptance in which participants were asked to what extent they would definitely get a COVID-19 vaccine, if it became available to them next week. Answers were obtained on a numeric scale ranging from "Strongly agree – 1" to "Strongly disagree – 5". To capture survey uncertainty, answers per age group were used to parameterise a multinomial distribution, from which we drew 100 replicates. To capture further uncertainty associated with the translation of survey response to vaccine uptake, for each replicate, coverage per age group was estimated assuming the probability of vaccination as a beta distribution with means: 0.98, 0.75, 0.50, 0.25 and 0.02 for survey responses 1, 2, 3, 4 and 5, respectively. Coverage distributions per age group, median as well as the 10% and 90% quantiles are shown in Table S5 and Fig. S2.

Mathematical model. We used a previously developed mathematical model for SARS-CoV-2 transmission and vaccination[7] (Fig. S1). The age-structured deterministic SEIR-type compartmental model incorporates an age-specific probability of infection determined by age-based contact matrices. Susceptible individuals become infected at a rate that depends on the level of infection in the community. Following infection, cases proceed to mild infection or a clinical disease pathway, which includes hospitalisation, oxygen support and intensive care. Waning immunity is captured by recovered individuals returning to the susceptible compartment following an erlang distribution.

Vaccination is modelled as an additional dimension disaggregating the population into those who have not received the vaccine (v0), those who have received the vaccine but are not yet protected (this stage represents the two-dose vaccine schedule and the need to wait ~28 days from dose 1 for protection to develop) (v1 and v2), those who have received the vaccine and are protected (v3 and v4) and those who have received the vaccine but are no-longer protected (v5) (if vaccine-derived immunity is not life-long). In this model, only those who are currently infected do not receive the vaccine. Protection due to vaccination is modelled at two stages in the model; (1) reducing the probability of infection upon exposure (efficacy against infection) and (2) reducing the probability of hospitalisation being indicated after developing disease (efficacy against hospitalisation and death).

Parameters. Parameters for SARS-CoV-2 infection, health care capacity, age-distribution and contact patterns are based on previous work[7,13] (Tables S1 and S4). Given these parameters, transmission probability is estimated based on reproductive number (Rt), which is given as an input for each simulation as a function of time. Vaccine-induced immunity was assumed lifelong, while natural immunity was assumed to last for an average of one year[14]. To produce simulations representing the different vaccines approved to date, each scenario was run for two vaccines: one with high efficacy (94% efficacy against infection[2]) and one with moderate efficacy (63% efficacy against infection[3]). For both vaccines we assume an additional 60% efficacy against hospitalisation for breakthrough infections, resulting in an overall vaccine efficacy against hospitalisation and death of 98% for

the high efficacy vaccine and 85% for the moderate efficacy vaccine. A summary of key parameters is given in Tables S1–S6. The model code is freely available at https://github.com/mrc-ide/nimue[15].

To mimic current vaccine rollout plans, vaccination is introduced in the population at the beginning of January 2021. We assumed a constant vaccination rate (κ), at which all individuals aged 15 years and above (~78% of the population) will be vaccinated over a 10-month period. This rate is implemented for all scenarios modelled, since we assume vaccination rate is constrained not by vaccine uptake but by the supply and delivery of vaccines. Therefore, lower levels of coverage, result in shorter vaccination campaigns; given that in the model, once coverage targets are met, vaccination is ceased. To illustrate the effect including children vaccination, vaccination rate was maintained constant and vaccination period was extended such that all individuals age 5–15 years could be vaccinated.

Vaccines are targeted by age groups at the constant rate κ, prioritising older age groups: with 80+ years vaccinated first and then sequentially including additional age groups in 5-year age-bands down to 15–19 years for adults only vaccination simulations and down to 5–10 years for simulations including children vaccination.

Reproductive number profiles. To simulate a representative pre-vaccination scenario, we generated a reproductive number profile in which Rt was the same as R_0 ($R_0 = 3$[13]) up to April 2020, subsequently decreased to 1 to represent the impact of NPIs against the first wave, and then rose to 1.5 during the latter half of 2020 to represent a second wave. Following the introduction of vaccination in January 2021, we set Rt to increase in 10 fixed steps. Each step representing the lifting of NPIs. The time for each step increase was determined by estimating when vaccination coverage had reached levels such that the herd immunity threshold due to vaccine immunity was reached. At the end of the vaccination period, R_t remained at a value such that the herd immunity threshold was maintained, given final vaccination coverage and vaccine efficacy against infection.

To estimate the coverage needed for each Rt step, the following herd immunity threshold equation was used:

$$\text{Coverage} = \left(1 - \frac{1}{R_t}\right)\frac{1}{\text{efficacy}}$$

When analysing the impact of lifting NPIs, the Rt profile following the introduction of vaccination was generated based on an ideal scenario for vaccination uptake. Conversely, when evaluating the degree to which NPIs would need to remain in place, the Rt profile after the introduction of vaccination was set up based on vaccine coverage due to vaccine hesitancy.

Scenarios. We consider two potential scenarios for vaccine coverage target per age group: an ideal scenario 2020 with 20 cases. A simulation was run for each vaccine coverage scenario for both adult-only vaccination campaign and vaccination campaign including children. As an output for each simulation, we estimated the number of deaths and hospitalisations associated with COVID-19 over the 2-year period from 1 January 2021 to 31 December 2022.

To generate country-specific simulations, we parameterise the model with data on the population size and age distribution of the country (https://population.un.org/wpp/) and representative contact matrices obtained from a systematic review of social contact surveys through the socialmixR package (https://github.com/sbfnk/socialmixr). The model was then fitted to reported daily cases and deaths up to 31 December 2020 by varying three parameters - the start date of the epidemic, the initial R0 and the effect size of changes in mobility on transmission (using mobility data from Google (https://www.google.com/covid19/mobility)). Model fitting was performed using a Metropolis Hastings MCMC based sampling scheme as previously described[16]. The resulting fit generates a fitted R0 as baseline, an Rt trajectory up to the introduction vaccination in January 2021, after which, Rt was set to increase by 10 fixed steps, up to the theoretical herd immunity threshold based on an ideal vaccination schedule (as described above). The pandemic trajectory was evaluated using country-specific data on vaccine hesitancy and demography for the two coverage scenarios described above and assuming vaccination for individuals aged 15 years and above only.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Results

Vaccine hesitancy public health impact. We first sought to determine the public health impact of vaccination and vaccine hesitancy as NPIs are lifted. To do so, we allowed the time-varying reproductive number in the absence of immunity R_t, to be increased in steps such that the herd immunity threshold accounting for vaccine-induced immunity was maintained, under the assumption of ideal vaccination uptake (Fig. 1a, c). In this ideal scenario, NPIs can be fully lifted at the end of the vaccination period with a high efficacy vaccine (94% efficacy, Fig. 1a). However, with a moderate efficacy vaccine (63% efficacy), some NPIs or other population-level behavioural changes may need to remain to control the epidemic (Fig. 1c).

In the presence of vaccine hesitancy, lifting NPIs and relying on vaccine-induced immunity for control is predicted to lead to periodic outbreaks determined by the duration of naturally induced immunity (Fig. 1b, d). For a high efficacy vaccine, daily deaths per million at the peak of the first outbreak are projected to be 11.5 (10.1–13.2) times higher than under the ideal scenario (Fig. 1b). This translates to a cumulative impact of 532 (457–612) more deaths per million population in the two years after vaccination begins. In our results, fewer deaths are projected for a vaccine of moderate efficacy compared to a higher efficacy vaccine. This is partly due prolonged NPIs being required to maintain herd immunity where efficacy is lower, resulting in an outbreak that is more spread out and resulting in a lower final Rt compared to the high vaccine efficacy simulations. For a moderate efficacy vaccine, the cumulative impact of vaccine hesitancy is projected to lead to 456 (416–504) extra deaths per million population.

These adverse impacts of vaccine hesitancy on transmission, symptomatic disease, hospitalisations and deaths affect vaccinated as well as unvaccinated individuals because of imperfect vaccine efficacy (Fig. 2). Under the vaccine hesitancy scenario, the resulting lower vaccination coverage is projected to lead to a 16.7% and 30.4% increase in hospitalisations in the vaccinated population for the high and moderate vaccine efficacy profile, respectively, and a 9.4% and 27.2% increase in deaths in the vaccinated population, compared to an ideal vaccination scenario (Fig. 2).

Relaxation of NPIs. As an alternative way to assess the impact of vaccine hesitancy on the pandemic, we evaluated the degree to which other NPIs would need to remain in place given the real-time achieved vaccine coverage in order to prevent further epidemics (i.e. maintain herd immunity threshold, Fig. 3). For the high efficacy vaccine, under the ideal scenario, we predict that NPIs could be fully lifted by the end of 2021 whilst keeping transmission under control (Fig. S3). However, under the vaccine hesitancy scenario, limited NPIs or other behavioural

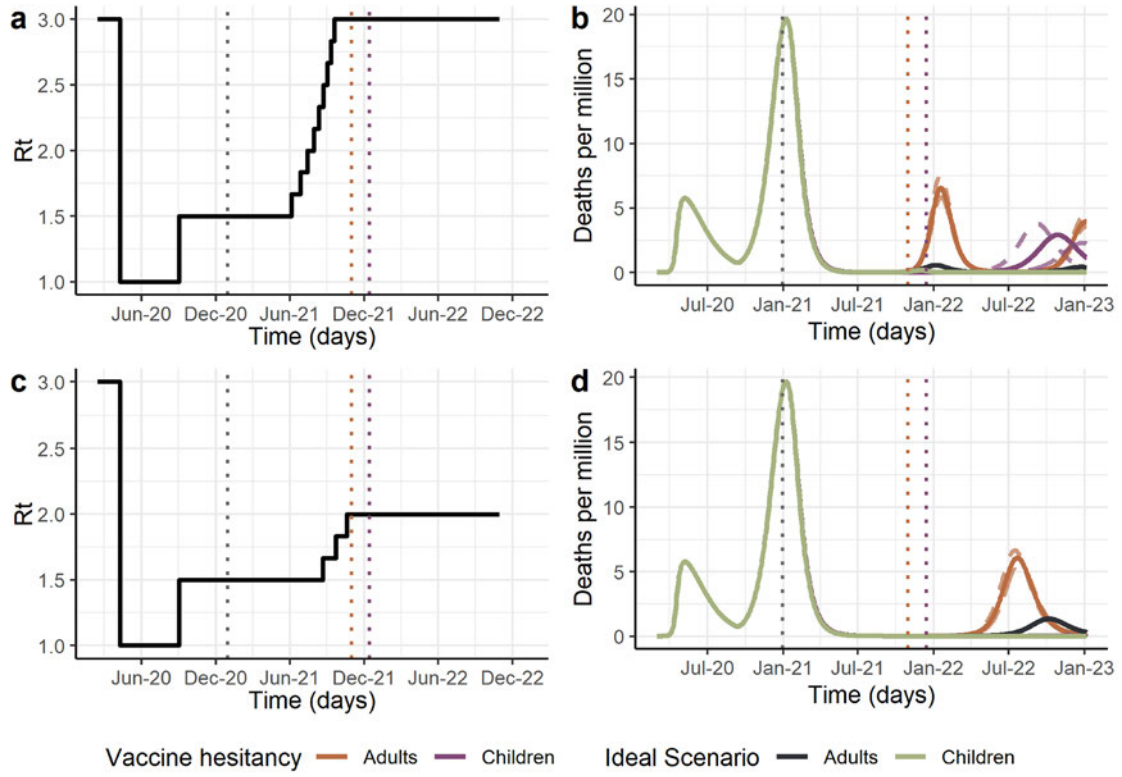

Fig. 1 Projected COVID-19 dynamics given vaccine hesitancy. Panels **a**, **b** show a high vaccine efficacy (94% against infection, 98% against hospitalisation and death), panels **c**, **d** moderate vaccine efficacy (63% against infection, 85% against hospitalisation and death). Panels **a** and **c** show the reproductive number Rt profile, which represents the level of NPI stringency, with lower numbers indicating higher stringency. In this illustrative example, we assume that a first wave of transmission occurred at the beginning of 2020 with the assumed value of Ro: 3. This was followed by NPIs leading to a reduction in Rt to 1, followed by an Rt of 1.5 as NPIs are lifted leading to a second wave of transmission in the latter half of 2020. After vaccination is introduced at the beginning of 2021, NPIs in all scenarios are lifted according to a schedule based on coverage under the ideal scenario (no vaccine hesitancy, 95% of individuals 15 years plus are vaccinated). Panels **b** and **d** show projected deaths per million under vaccine hesitancy scenarios: adults-only vaccination (orange), vaccination including children (purple). Continuous lines represent simulations of median vaccine coverage per age group, while dashed lines represent simulation of 10% and 90% quantiles. For the ideal scenario black line represents adults-only vaccination and green line represents ideal scenario when children vaccination is considered. In each scenario, final vaccination coverage per age group and deaths vary according to vaccine hesitancy. Vertical dashed lines indicate the vaccination rollout period in the ideal scenario.

modifications might need to remain in place, with Rt having to stay below 2.05 (1.96–2.14) to prevent further epidemics, this represents a 32% reduction of the assumed R0 of 3. A difference of ~35% in the effective reproductive number could represent the closure of educational institutions or limiting interaction between households to achieve control of the epidemic;[17] both of which are not sustainable or desirable.

Vaccination of children. As current vaccination rollout plan of adults continues swiftly in most high-income countries, public health authorities are now looking to include children into their vaccination campaigns while results of COVID-19 vaccine efficacy in children become available[18]. To evaluate the impact of including children in vaccination rollouts, we model all scenarios with a longer vaccination campaign, which allowed individuals above 5 years old to get vaccinated, assuming vaccine hesitancy for 5–17 years old the same levels reported for 18–24 years old[10]. If children are included in vaccine rollout, our results illustrate that in a scenario with vaccine hesitancy daily deaths per million at the peak of the first outbreak could be reduced by 56% (51–60%) for a vaccine with high efficacy (Fig. 1b). Which implies a total reduction of 272 (242–346) deaths per million in the two years after vaccination begins (Fig. S4). For a moderate vaccine efficacy, higher NPIs stringency at the end of vaccine rollout entails later outbreaks, which do not take place during the two years after vaccination begins, resulting in similar results for the ideal and vaccine hesitancy scenario when including the vaccination of children (Fig. 1d and S4). Including children in vaccine rollout leads to higher vaccine coverage that compensates for vaccine hesitancy levels in adults. This is evident when evaluating the degree to which other NPIs would need to remain in place in order to maintain the herd immunity threshold based on vaccine-acquired immunity levels. For a high efficacy vaccine, in a vaccine hesitancy scenario Rt levels can increase up to 2.5 (Fig. 3b), ~20% more than for adult-only vaccination rollout. This increase entails milder NPIs at the end of vaccination campaign.

Country-specific simulations. Our illustrative examples above are comparable to the waves of COVID-19 outbreaks in Europe. However, vaccine hesitancy varies between countries. To evaluate the impact of these variations, we chose three European countries with different vaccine acceptance views: France, Germany and the United Kingdom (UK) (Fig. 4b). For each country, we fit the pandemic trajectory to country-specific data up to vaccination

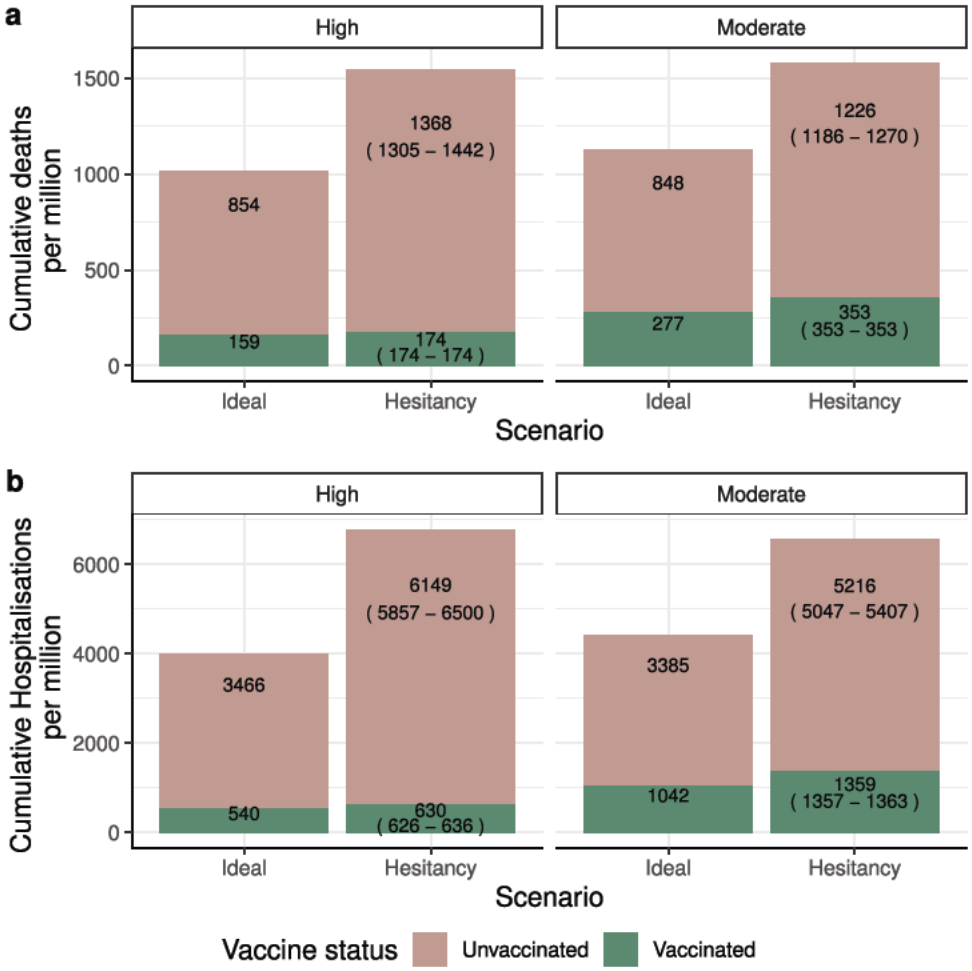

Fig. 2 Public health impact of vaccine hesitancy. High vaccine efficacy is shown on the left and moderate vaccine efficacy on the right. The annotated numbers are the cumulative deaths (**a**) and hospitalisations (**b**) per million individuals for the vaccinated and unvaccinated populations at the end of the projection horizon (1 January 2021–31 December 2022). Vaccination coverage of individuals aged 15 years and older is highest in the ideal scenario at 95%. For the hesitancy scenario annotated number is for median vaccine coverage per age groups, number in parenthesis are results for 10% and 90% quantiles coverage per age group.

started (1 January 2021), after which we model the trajectory of the pandemic under an ideal vaccination and a vaccine hesitancy scenario for each country independently (Fig. 4c)

For a vaccine with high efficacy, we project 1.2 (1.1–1.3), 5.0 (4.0- 6.3)- and 6.6 (5.7–7.6) times more deaths in 2021/2022 in a scenario with hesitancy compared to an ideal scenario in the UK, Germany and France respectively (Fig. 4a Death ratios vary between age groups, vaccine efficacy and countries depending on deaths predicted in their corresponding ideal scenarios. Nonetheless, for both high and moderate vaccine efficacy, the highest impact on total deaths is for the oldest age groups and it increases in countries with higher vaccine hesitancy (Figs. S5 and S6).

Discussion

We have examined the effects of low vaccine uptake due to vaccine hesitancy for the current COVID-19 pandemic and have shown the impact of vaccine hesitancy, detailing the considerable mortality that could be averted with increased vaccine coverage. Our results have demonstrated that including less vulnerable groups, like children, can reduce the impact of vaccine hesitancy for current vaccination campaigns. These results further support the idea of the indirect benefits of vaccination, which are necessary to achieve herd immunity[7,19]. However, the control of the pandemic as reduction of severe cases (i.e., hospitalisations) and mortality, does not only depend on vaccine uptake but vaccine efficacy and stringency levels of NPIs[7,20,21], which we have represented as underlying transmissibility (Rt). Our simulations confirm, that vaccination alone is unlikely to control the current pandemic and NPIs still have a large impact on the epidemic trajectories, until sufficient coverage is reached[22]. In a scenario with lower vaccine efficacy and vaccine hesitancy, longer and more stringent NPIs would be required to compensate lower efficacy as higher coverage levels are required to achieve herd immunity[19].

Our model structure allowed us to capture vaccine hesitancy heterogeneity between age groups[9–11] and analyse its effect in current vaccine rollout plans, which are prioritising older individuals. We have shown that even though older age groups have higher vaccine acceptance levels, these groups have higher mortality in a vaccine hesitancy scenario. As our model does not capture differential risk within sub-populations, it was not possible to assess the effect of vaccine hesitancy in other prioritised populations like health care workers. In which high levels of vaccine hesitancy have been reported despite having higher risk of infection[23].

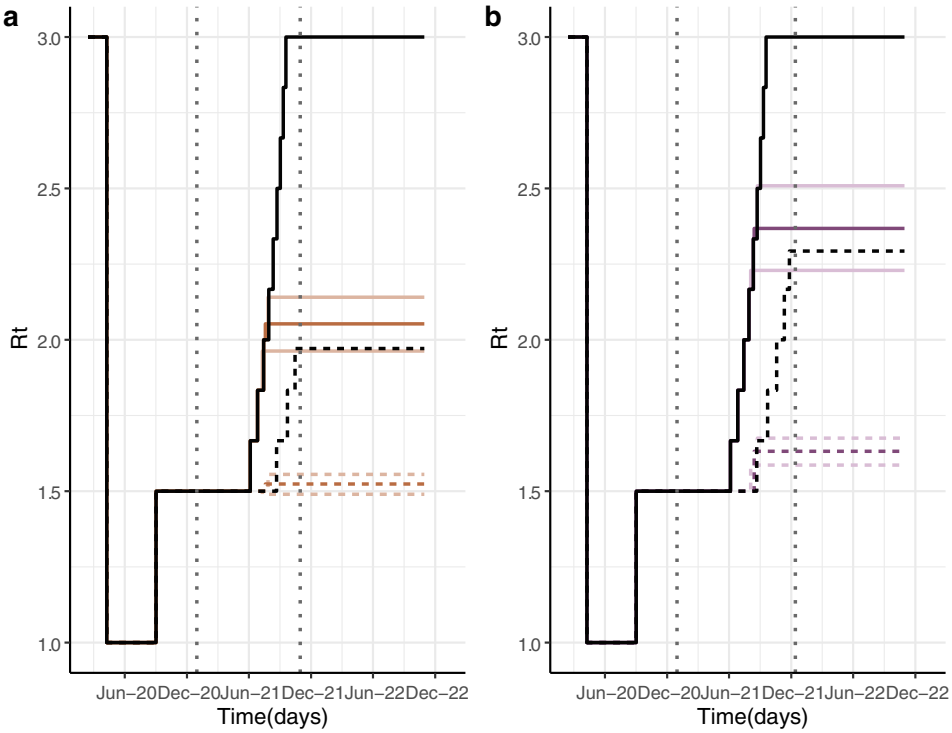

Fig. 3 Stringency of NPIs required to control the epidemic under different vaccine hesitancy scenarios. Panel **a** shows Rt profiles for an adults-only vaccination campaign. Panel **b** shows Rt profiles for a vaccination campaign including children. Reproductive number profiles are estimated to keep the herd immunity threshold such that epidemic impact is the same for each scenario as in the ideal scenario. A lower reproductive number corresponds to more stringent NPIs. Continuous lines represent profiles for a high efficacy vaccine and dashed lines represent profiles for a moderate efficacy vaccine. Vertical dotted lines show the period of vaccination in the ideal scenario.

Country fitting showed a higher initial Rt compared to our illustrative example. These values are consistent with those estimated for other European countries, where initial Rt values have been estimated as high as ~4.5, which may be due to possible under-ascertainment in deaths in early periods of the pandemics[1]. It is still unknown how transmission levels will develop in the long term as more transmissible variants are emerging and NPIs behaviour may persist after the pandemic. Here we have assumed a staged release of NPIs with a step-wise increase of Rt, representing governments' easing of restrictions. This step function is a simplification to illustrate the process of balancing the relaxation of NPIs whilst continuing to suppress transmission. Nonetheless, the evaluation approaches introduced in this study can be adjusted to include complex Rt dynamics as more information on COVID-19 transmissibility evolution become available.

Our analysis necessarily makes many simplifying assumptions, and it is important to note that the future trajectory of the epidemic will depend on the complex interactions between vaccination uptake, behaviour and government interventions. First, we have assumed homogenous mixing between vaccine-hesitant individuals. However, as has been seen for other diseases, COVID-19 vaccine hesitancy is heterogenous and clustered within population subgroups[24]. Transmission is more likely to be sustained within clusters with low vaccine coverage[25,26] and therefore future outbreaks may be limited to these sub-populations. Secondly, we have modelled hesitancy levels constant over the time frame analysed; yet, self-reported attitudes to COVID-19 vaccines are changing over time[9,10] as the perceived risk for both disease and vaccines keeps varying[12,21]. Thirdly, we have assumed vaccination rate remains constant over the vaccination period. However, vaccination logistics depend on multidisciplinary factors[27] and both vaccine availably and uptake can be dynamic. Finally, our model does not account for immune escape from the vaccine due to new variants arising. Whilst second-generation vaccines will likely become available to address this issue, it is currently unclear whether some of the high levels of vaccine uptake observed in early vaccine rollouts would be sustained in subsequent booster programmes.

Getting vaccinated is an individual choice, but these individual choices have population wide effects that are likely to challenge current efforts to control COVID-19. Our findings suggest that vaccine hesitancy may have a substantial impact on the pandemic trajectory, deaths and hospitalisation. To prevent such adverse outcomes, NPIs would need to stay in place longer, or possibly indefinitely, resulting in high economic and social costs[28,29]. Reducing vaccine hesitancy is therefore an important public health priority. Interventions that aim to build trust, for example with community-based public education or via positive role-models, are proven efficacious approaches to address hesitancy[30]. There is an ongoing debate about vaccine passports as a condition to travel, or a vaccination requirement for employees[31]. Such interventions may be effective because they incentivize individuals to get vaccinated, but they are controversial in libertarian democracies because they curtail personal freedom and individual choice about medical treatments. The alternative will be to accept some level of disease, hospitalisation and deaths given the level of vaccine coverage achieved whilst allowing NPIs to be lifted, given that NPIs are not a sustainable long-term method for control.

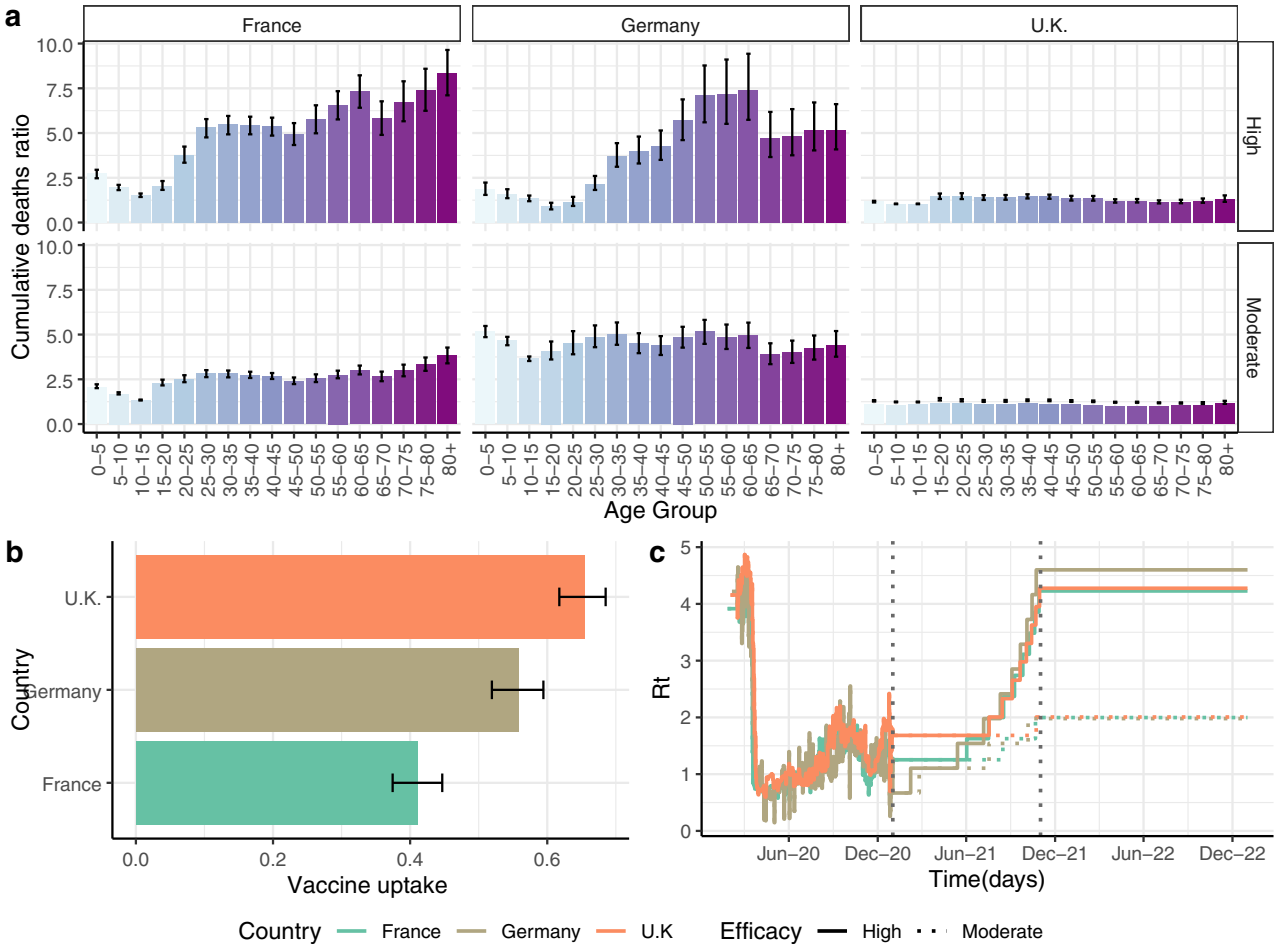

Fig. 4 Impact of vaccine hesitancy for three European countries. a Cumulative death ratios per age group compared to the ideal vaccine uptake scenario, by country and vaccine efficacy profile. The ratio compares cumulative deaths projected over a 2-year period after vaccination starts for two scenarios: an ideal scenario, where 95% of the population older than 15 years gets vaccinated and a vaccine hesitancy scenario, where coverage for people over 15 years old is based on vaccine acceptance from b. **b** Reported vaccine acceptance per age group in France, Germany and the United Kingdom reproduced from Jones et al[10]. Values show median vaccine coverage and bars show 10–90% quantiles obtained by running the model at the quantiles from the data. **c** Reproductive number profile for country-specific simulations. Profiles, before vaccination begins, are taken from model fittings to country-specific data (https://mrc-ide.github.io/global-lmic-reports/). After vaccination starts, NPIs are lifted based on an ideal vaccination coverage over time. Reproductive number is set to increase in ten steps from the value at the beginning of vaccination to an average initial reproductive number. Continuous lines show profiles for a high efficacy vaccine. Dotted lines show profiles for a moderate efficacy vaccine.

Data availability

All data used in this study are from publicly available sources at the links provided in the main text and references. Vaccine hesitancy surveys are from the Imperial College London YouGov Covid 19 Behaviour Tracker Data Hub (https://github.com/YouGov-Data/covid-19-tracker). For ease of reproducibility of our results, the dataset is also stored in our associated publicly available Github repository[32] so that the modelling outputs can be reproduced without further data manipulation. Demographic information is from the United Nations Population prospects https://population.un.org/wpp/). Mobility data from Google (https://www.google.com/covid19/mobility). And model fittings to country-specific data are from https://mrc-ide.github.io/global-lmic-reports/results. Source data can be found in the Supplementary Data file.

Code availability

Analyses were carried out in R 4.0.2. Code for the transmission model and analysis is available on GitHub[32]. COVID-19 vaccination model code is available at https://github.com/mrc-ide/nimue[15].

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Author contributions

A.C.G., K.H., P.W. and D.O.M. conceived the study. A.B.H., P.W., O.J.W. and G.D.C. developed and coded the model. D.O.M. ran the simulations and undertook the analysis with support from P.W.; O.J.W. parametrised the model to country data. D.O.M. produced the first draft of the manuscript with additional input from P.W., K.H. and A.C.G. All authors approved the final version for submission.

Competing interests

A.B.H., P.W. and A.C.G. declare consultancy fees from the World Health Organization in relation to modelling COVID-19 vaccine impact in the European region, outside the submitted work. The authors declare no other competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s43856-022-00075-x.

Correspondence and requests for materials should be addressed to Daniela Olivera Mesa.

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Exhibit H

Cureus

Open Access Review Article

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Unveiling the Impact of COVID-19 Vaccines: A Meta-Analysis of Survival Rates Among Patients in the United States Based on Vaccination Status

Review began 08/01/2023
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Anderson E. Ikeokwu [1], Rebecca Lawrence [1], Egbaoghene D. Osieme [1], Khalifa M. Gidado [2], Cullen Guy [3], Oladejo Dolapo [1]

1. College of Medicine, Richmond Gabriel University, Kingstown, VCT 2. School of Medicine, All Saints University Dominica, Roseau, DMA 3. College of Medicine, Washington University of Health and Science, San Pedro, BLZ

Corresponding author: Anderson E. Ikeokwu, ikeokwu.anderson@gmail.com

Abstract

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a significant number of cases and deaths worldwide. Vaccination is the most effective preventive measure against the disease. This study aimed to assess the mortality rates of COVID-19 patients in the United States and the effectiveness of Pfizer (Pfizer, NY, USA), Moderna (Moderna, MA, USA), and Janssen (Johnson & Johnson, NJ, USA) vaccines in preventing mortality.

A systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA-2020) guidelines. Eligible studies reporting on the effectiveness of COVID-19 vaccines on patient outcomes were included. The search was performed in PubMed, Cochrane, and Google Scholar databases. The data were extracted, and risk ratios (RR) were calculated for mortality outcomes. The analysis was performed using Review Manager software, and bias assessments were conducted using the Joanna Briggs Institute (JBI) Meta-Analysis tools.

A total of seven studies with 21,618,297 COVID-19 patients were included in the meta-analysis. The odds ratio (OR) for mortality among unvaccinated patients compared to vaccinated patients was 2.46 (95% CI: 1.71-3.53), indicating that unvaccinated patients were 2.46 times more likely to die from COVID-19.

The findings of this study support the effectiveness of COVID-19 vaccination in reducing mortality among infected individuals. Unvaccinated patients had a significantly higher risk of mortality compared to vaccinated patients. Vaccination remains a crucial strategy to mitigate the severity of the disease and reduce mortality rates. Efforts should be made to address vaccine hesitancy and ensure widespread vaccine coverage.

Categories: Internal Medicine, Infectious Disease, Public Health
Keywords: covid-19 vaccination, sars-cov-2, systematic review and meta analysis, corona virus disease 2019 (covid-19), mortality, north america, covid-19

Introduction And Background

Ever since the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, in December 2019, the world has witnessed close to 760 million confirmed cases of COVID-19 infection, and as a result close to seven million deaths as of May 2023. The WHO statistics tabulate 115 million confirmed cases and as a result 1.5 million deaths in the North American Region inclusive of the United States, Canada, and Mexico [1].

At this time, there continue to be new variants of the COVID-19 virus with increasing complications and mortality rates, thereby forcing researchers to find innovative ways to combat the disease's lethality therapeutically and with preventative efforts. Vaccination continues to be the most accessible and safest method to prevent future reinfections and improves clinical outcomes in the case of hospitalization.

The US Coronavirus vaccine tracker states that 81% of the population has received at least one dose of the vaccine, 70% received two doses and are considered fully vaccinated whereas an additional 34% of the population has received at least one booster dose [2]. However, a sizeable portion of the public is still reluctant to get the vaccine due to concerns about safety, emergency authorization of these vaccines, mistrust in their public health systems, or misplaced complacency [3]. Therefore, we conducted a systematic review and meta-analysis to examine mortality rates of American patients infected with COVID-19 and the effectiveness of the following vaccines namely Pfizer (Pfizer, NY, USA), Moderna (Moderna, MA, USA) and Janssen (Johnson & Johnson, NJ, USA) available to the public.

Review

How to cite this article
Ikeokwu A E, Lawrence R, Osieme E D, et al. (August 10, 2023) Unveiling the Impact of COVID-19 Vaccines: A Meta-Analysis of Survival Rates Among Patients in the United States Based on Vaccination Status. Cureus 15(8): e43282. DOI 10.7759/cureus.43282

Materials and methods

Study Design

To evaluate the acceptance rate of COVID-19 vaccination, a meta-analysis was performed on a collection of studies. The assessment adhered to the guidelines set forth by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA-2020) [4] to review the relevant articles. As the analysis solely utilized published data, no ethics review or approval was necessary.

Eligibility Criteria

The criteria for inclusion, include studies that report on the effectiveness of COVID-19 vaccination on patient outcomes with COVID-19 infection. The criteria included studies after the availability of COVID-19 vaccines. All types of COVID-19 vaccines utilized in the United States were included in this review.

Population (P): We included studies with cross-sectional, case-control, cohort designs and randomized controlled trials of any age published in English from 2020 to July 10, 2022 from the United States. Case series/reports, conference papers, proceedings, articles available only in abstract form, editorial reviews, letters of communication, commentaries, systematic reviews, and qualitative studies were excluded. Articles in languages other than English or study areas not in the United States were excluded.

Intervention (I): We included all types of COVID-19 vaccines utilized in the United States in this review.

Comparison (C): We included studies that compared the patients into two groups according to their vaccination status. Individuals who received at least one dose of any COVID-19 vaccine were placed in the "vaccinated group"; individuals who did not receive any vaccine dose were placed in the "non-vaccinated group."

Outcomes (O): Our primary outcome measures mortality due to COVID-19 infection.

Information Sources

A systematic search was conducted on April 21, 2022, utilizing three databases: PubMed, Cochrane, and Google Scholar. To identify additional relevant studies, a "snowball" search strategy was employed by examining the reference lists of publications eligible for full-text review and screening studies that cited them using Google Scholar. The database search was further updated on July 7, 2022, while the snowball and additional searches were conducted on July 8, 2022.

Search Strategy

The search was done using the generic free-text search terms developed based on the study, Patient-Intervention-Comparison-Outcome (PICO) model to define the clinical question to aid in finding clinically relevant evidence in the literature. P = "COVID-19" AND "UNITED STATES," I = "COVID-19 VACCINE," C = "VACCINATION STATUS" OR "VACCINATED" AND "UNVACCINATED," O = "MORTALITY." In order to encompass all possible and relevant studies, a broad range of search terms was utilized. All studies published between 2020 and July 10, 2022 were gathered to determine their suitability for inclusion in this study. The search was limited to full-text articles written in English. To identify any additional studies that met the inclusion criteria, the reference lists of the included citations were carefully examined.

Selection Process

Our search strategy yielded a collection of records that were exported to Rayyan Intelligent Systematic Review software (Rayyan System Inc., MA, USA) [5]. This software helps ensure data integrity by removing all duplicate articles. The initial examination of the titles and abstracts of the first 100 records was conducted independently by two researchers (AI and RL). Any disparities encountered were discussed until a consensus was reached. Subsequently, the researchers worked in pairs to evaluate the titles and abstracts of all retrieved articles. In the event of discordance, a consensus on which articles to review in the full text was achieved through discussion. If necessary, a third researcher (EO) was consulted for assistance in making the final decision. Afterward, the full-text articles were individually reviewed for inclusion by both researchers (AI and RL). Again, any differences in opinion regarding inclusion or exclusion were resolved through discussion. The search methodology employed is depicted in the PRISMA flow chart (Figure *1*), which illustrates the included studies as well as those excluded along with the reasons for exclusion. The reasons for exclusion included: Reason 1: absence of comparable groups (i.e., vaccinated vs. unvaccinated), Reason 2: unavailability of the complete text, and Reason 3: lack of relevance to the research question, encompassing insufficient data on patient health outcomes.

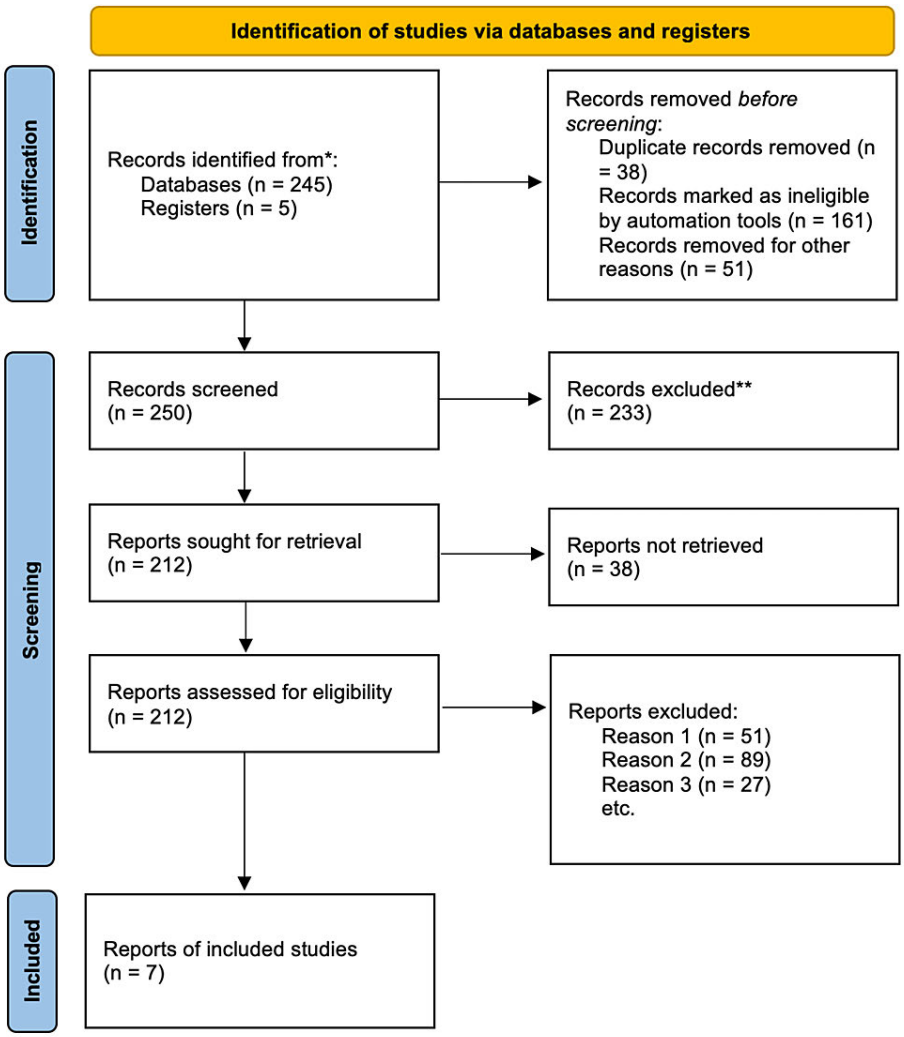

FIGURE 1: PRISMA flow diagram showcasing the inclusion criteria of studies found eligible in the meta-analysis

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

Data Collection Process

We designed a data extraction form based, on which two review authors (AI and RL) used to extract data from eligible studies. Extracted data were compared, with any discrepancies being resolved through discussion. The data was entered into Review Manager (RevMan 2014) Version 5.3 (Cochrane, Copenhagen, Denmark) [6], double-checking this for accuracy.

Data Outcomes

The data included the first author, the year the study was published, the study's location, its design, the setting, the characteristics of the COVID-19 patients who participated in the trial and their various comorbidities, the number of doses, the sample size, the proportion, and information needed to assess the effect estimates. Death from COVID-19 infection was the specific outcome measure that was recorded for the meta-analysis. Mortality from SARS-CoV-2 was defined as death within 28 days of first testing positive for SARS-CoV-2 via PCR test [7]. The effectiveness of a COVID-19 vaccine was referred to in this study as to how well the vaccine works in preventing COVID-19 infection or reducing the severity of the disease among vaccinated individuals. It was typically measured in this study by comparing the rates of mortality between vaccinated and unvaccinated patients with COVID-19 infection.

Effect Measures

The effectiveness of COVID-19 vaccination on patient outcomes with COVID-19 infection was reported in

pooled estimate proportion with a 95% confidence interval. We analyzed dichotomous outcomes by calculating the odds ratio (OR) of a patient outcome (i.e., mortality) for each study.

Synthesis Methods

The analysis was performed with the software RevMan 2014. A generic inverse variance with a random-effects model was applied to pool the proportion of the studies' data. The heterogeneity was assessed by I2 statistic and p-value. If the p-value is < 0.05 or I2 > 50%, the assumption of homogeneity was rejected, and a random-effects model was adopted.

Study Risk of Bias Assessment

The risk of bias assessment was assessed using the Risk of Bias tool 2.0 (RoB 2.0) (Cochrane, London, United Kingdom) to assess the risk of bias for each of the included observational studies [8]. The evaluation of data quality was conducted using the Joanna Briggs Institute (J.B.I.) to critically appraise the studies included in the meta-analysis. The meta-analysis encompassed cross-sectional, case-control, cohort studies, and randomized clinical trials [9]. The risk of bias in the observational studies (case-control and cohort) was evaluated using nine criteria [9]: (1) appropriateness of the sample frame, (2) appropriateness of the sampled study participants, (3) adequacy of the sample size, (4) description of the study subjects and setting, (5) justification of sample size, power description, or variance and effect estimates, (6) valid methods for identifying the condition, (7) standardized and reliable measurement of the condition, (8) appropriateness of statistical analysis, and (9) adequacy of the response rate. The risk assessment criteria were categorized as "yes," "no," "unclear," or "not available." A score of one (1) was assigned for "yes" responses, while a score of zero (0) was given for the remaining categories. The risk of bias was considered low when the total score exceeded 70%, moderate when it ranged from 50% to 69%, and high when it fell between 0% and 49% [9]. Two authors independently performed the bias assessments.

Rating Evidence of Quality

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to rate the quality of evidence the clinical outcome (mortality from COVID-19 infection), as high, moderate, low or very low [10]. The assessment included judgments addressing the risk of bias, imprecision, inconsistency, indirectness, and publication bias low [10]. If there were serious concerns in any of these domains (for instance, in risk of bias), we rated the quality of the evidence low [10]. The GRADEpro Guideline Development Tool (GDT) software (McMaster University, ON, Canada and Evidence Prime, Kraków, Poland) was utilized to rate the quality of evidence [11].

Results

We identified 250 published papers in database searching. Across all of these papers, there were 21,618,297 COVID-19 patients. A total of 240 articles from PubMed and 10 from the Cochrane database were identified from the initial search. Following duplicate removal, 167 articles were excluded in accordance with the inclusion and exclusion criteria. We finally selected seven articles for the meta-analysis (Table *1*).

Author (Year)	Study Area	Study Type Design	Journal name	Total number of patients	Outcomes analyzed	Vaccine type
Naleway (2021) [12]	USA	Retrospective Cohort	MMWR (CDC)	482,464	HR, MV, CC, ICU, MR	Pfizer, Moderna, Janssen (J&J)
Johnson (2022) [13]	USA	Retrospective Cohort	MMWR (CDC)	9,678,557	CC, MR	Unspecified
Danza (2022) [14]	USA	Cross-sectional	MMWR (CDC)	422,966	HR, MV, ICU, MR,	Pfizer, Moderna, Janssen (J&J)
Olson (2022) [15]	USA	Case-control	The New England Journal of Medicine	1,222	HR, VT, ICU, MR	Pfizer
Griffin (2021) [16]	USA	Cross-sectional	MMWR (CDC)	43,127	HR, MV, CC, ICU, MR	Pfizer, Moderna, Janssen (J&J)
Tenforde (2022) [17]	USA	Case-control	Jama Network	1,983	HR, MR,	Pfizer, Moderna
Xu (2021) [18]	USA	Retrospective Cohort	MMWR (CDC)	10,987,919	MR	Pfizer, Moderna, Janssen (J&J)

TABLE 1: Sample size of selected studies and their characteristics

MMWR: Morbidity and Mortality Weekly Report, CDC: Centers for Disease Control and Prevention, HR: Hospitalization rate, MV: Mechanical ventilation, CC: COVID-19 cases, ICU: Intensive care unit, MR: Mortality rate, VT: Tidal volume

In a review examining the effectiveness of COVID-19 vaccination on patient outcomes with COVID-19 infection, the authors included a table presenting for each included study the citation, study design, country, sample size, median age, male: female and ethnicity distribution of vaccinated and unvaccinated patients, patient comorbidities, and type of COVID-19 vaccine used of various studies have been elaborated in Tables *2*-*6*. In this analysis, mortality in various studies is considered a clinical outcome in patients with COVID-19 infections.

Author (Year)	Total number of patients	N (%) Vaccinated	N (%) Unvaccinated	N (%) Female	N (%) Male	Age Range of patients
Naleway (2021) [12]	482,464	344,848 (71.5)	137,616 (28.5)	251,552 (52.1)	230,552 (47.8)	18-75
Johnson (2022) [13]	9,678,557	2,866,517 (29.6)	6,812,040 (70.4)	-	-	18-65+
Danza (2022) [14]	422,966	281,038 (66.4)	141,928 (33.6)	224,173 (53)	184,134 (43.5)	18-80+
Olson (2022) [15]	1,222	345 (28.2)	868 (71.8)	-	-	12-18
Griffin (2021) [16]	43,127	12,326 (28.6)	30,801 (71.4)	21,743 (50.4)	20,425 (47.4)	16-80+
Tenforde (2022) [17]	1,983	314 (15.8)	1,669 (84.2)	969 (48.9)	1,014 (51.1)	18-65+
Xu (2021) [18]	10,987,919	6,398,361 (58.2)	4,589,557 (41.8)	5,946,533 (54.1)	5,041,385 (45.9)	12-85+

TABLE 2: Summary of demographics data

N: Number of patients vaccinated/unvaccinated, %: Percentage of patients vaccinated/unvaccinated in relation to the total number of patients

Author (Year)	N (%) Vaccinated	N (%) Female	N (%) Male	Mean/Median age	N (%) White	N (%) Asian	N (%) Black	N (%) Hispanic	N (%) Native American	N (%) Native Hawaiian/pacific islander	N (%) Multiple races/others/unknown
Na eway (2021) [12]	344,848	187,711 (54.5)	156,960 (45.5)	50	242,110 (70.2)	22,828 (6.6)	8,224 (2.4)	-	1,2880 (0.4)	1,931 (0.6)	68,475 (19.9)
Johnson (2022) [13]	2,866,517	-		-	-	-	-	-	-	-	-
Danza (2022) [14]	281,038	154,791 (55.1)	117,971 (42)	36	46,612 (16.6)	26,384 (9.4)	15,991 (5.7)	-	530 (0.2)	2,348 (0.8)	40,538 (14.4)
O son (2022) [15]	345	-	-	16	143 (41.4)	-	68 (19.7)	94 (27.2)	-	-	49 (14.2)
Gr ff n (2021) [16]	12,326	6,271 (50.9)	5,908 (47.9)	36	3,718 (30.2)	1,009 (8.2)	819 (6.6)	3,961 (32.1)	19 (0.2)	49 (0.4)	2,447 (19.9)
Tenforde (2021) [17]	314	138 (44)	176 (56)	67	201 (64)	-	55 (17.5)	44 (14)	-	-	14 (4.5)
Xu (2021) [18]	6,398,361	3,448,362 (53.9)	2,949,999 (46.1)	-	2,778,730 (43.4)	633,212 (10)	341,189 (5.3)	1,409,187 (22)	-	-	880,523 (13.8)

TABLE 3: Summary of demographics data for vaccinated patients

N: Number of patients vaccinated/unvaccinated, %: Percentage of patients vaccinated/unvaccinated in relation to the total number of patients

Author (Year)	N (%) Unvaccinated	N (%) Female	N (%) Male	Mean/Median age	N (%) White	N (%) Asian	N (%) Black	N (%) Hispanic	N (%) Native American	N (%) Native Hawaiian/pacific islander	N (%) Multiple races/others/unknown
Na eway (2021) [12]	137,616	63,841 (46.4)	73,592 (53.5)	37	83,474 (60.7)	3,930 (2.9)	4,851 (3.5)	-	588 (0.4)	1,021 (0.7)	43,752 (31.8)
Johnson (2022) [13]	6,812,040	-	-	-	-	-	-	-	-	-	-
Danza (2022) [14]	141,928	69,382 (48.9)	66,163 (46.6)	35	20,529 (14.5)	7,451 (5.2)	12,319 (8.7)	-	342 (0.2)	1,429 (1)	19,214 (1305)
O son (2022) [15]	868	-	-	15	358 (41.2)	-	197 (22.7)	191 (22)	-	-	122 (14)
Gr ff n (2021) [16]	30,801	15,472 (50.2)	14,517 (47.1)	32	5,620 (18.2)	961 (3.1)	4,755 (15.4)	10,183 (33.1)	51 (0.2)	161 (0.5)	8,551 (27.8)
Tenforde (2021) [17]	1,669	831 (49.8)	838 (50.2)	53	717 (43)	-	453 (27.1)	381 (22.8)	-	-	118 (7.1)
Xu (2021) [18]	4,589,557	2,498,171 (54.4)	2,091,386 (45.6)	-	1,982,834 (43.2)	633,212 (13.8)	262,766 (5.7)	1,201,784 (26.2)	-	-	508,961 (11.1)

TABLE 4: Summary of demographics data for unvaccinated patients

N: Number of patients vaccinated/unvaccinated, %: Percentage of patients vaccinated/unvaccinated in relation to the total number of patients

Author (Year)	Total number vaccinated	N (%) chronic kidney disease	N (%) Diabetes	N (%) Chronic lung disease	N (%) cardiovascular disease	N (%) Immunodeficiency disorder	N (%) Neuromuscular/Neurological disorder
Naleway (2021) [12]	344,848	32 (0.009)	24 (0.007)	24 (0.007)	-	-	-
Johnson (2022) [13]	2,866,517	-	-	-	-	-	10 (0.0003)
Danza (2022) [14]	281,038	-	-	-	-	-	-
Olson (2022) [15]	345	-	28 (8.1)	81 (23.5)	27 (7.8)	-	-
Griffin (2021) [16]	12,326	-	-	-	-	-	-
Tenforde (2021) [17]	314	-	112 (35.7)	100 (31.8)	236 (75.2)	128 (40.8)	-
Xu (2021) [18]	6,398,361	-	-	-	-	-	-

TABLE 5: Summary of patient comorbidities for vaccinated patients

N: Number of patients vaccinated/unvaccinated, %: Percentage of patients vaccinated/unvaccinated in relation to the total number of patient

Author (Year)	N (%) Unvaccinated	N (%) chronic kidney disease	N (%) Diabetes	N (%) Chronic lung disease	N (%) cardiovascular disease	N (%) Immunodeficiency disorder	N (%) Neuromuscular/Neurological disorder
Naleway (2021) [12]	137,616	37 (0.03)	98 (0.07)	22 (0.02)	-	-	-
Johnson (2022) [13]	6,812,040	-	-	-	-	-	15 (0.0002)
Danza (2022) [14]	141,928	-	-	-	-	-	-
Olson (2022) [15]	868	-	72 (8.3)	241 (27.8)	69 (8)	-	-
Griffin (2021) [16]	30,801	-	-	-	-	-	-
Tenforde (2021) [17]	1,669	-	425 (25.5)	327 (19.6)	814 (48.8)	191 (11.4)	-
Xu (2021) [18]	4,589,557	-	-	-	-	-	-

TABLE 6: Summary of patient comorbidities for unvaccinated patients

N: Number of patients vaccinated/unvaccinated, %: Percentage of patients vaccinated/unvaccinated in relation to the total number of patients

Risk of Bias Assessment

In terms of overall risk bias, the risk of bias was low. There were concerns about the uncertain risk of bias in two out of the nine criteria for all seven studies included. These two criteria were justification of sample size and adequacy of response rate. All of the studies did not report enough data to justify the sample size or assess the adequacy of the response rate. Regarding the adequacy of sample size, one study [15] was at high

risk of bias. A summary of these assessments is provided in Figure 2.

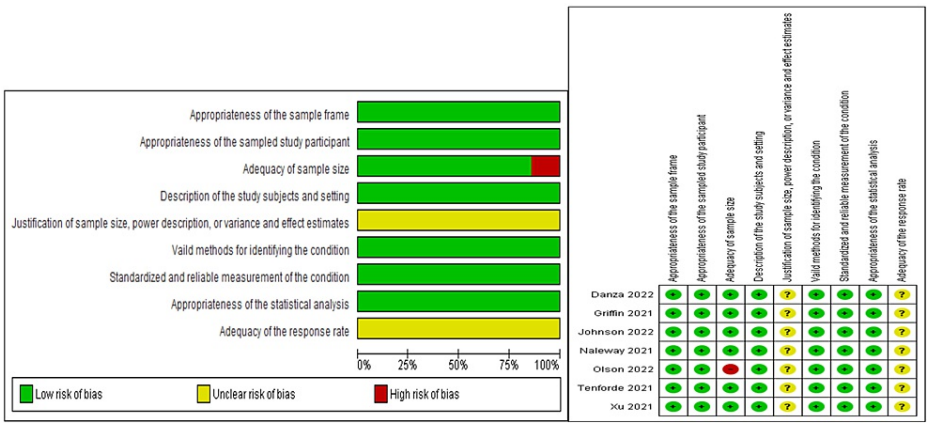

FIGURE 2: Risk bias assessment

Analysis of Mortality From COVID-19 by Vaccination Status

The patient outcomes in COVID-19 patients were compared between those who received the COVID-19 vaccine and those who did not. In the seven studies analyzed, a total of 139,485 patients were reported to have died from COVID-19 infection. The OR of COVID-19 mortality between patients with COVID-19 vaccination versus patient without COVID-19 vaccination was 2.46 with a 95% CI ranging from 1.71 to 3.53. The result was statistically significant which indicates that unvaccinated patients with COVID-19 infection are 2.46 times more likely to die from COVID-19 infection compared to those who are vaccinated with COVID-19 infection ($p < 0.0001$). A heterogeneity test was done with results of $I2 = 100\%$, $p = <0.00001$ (Figure 3).

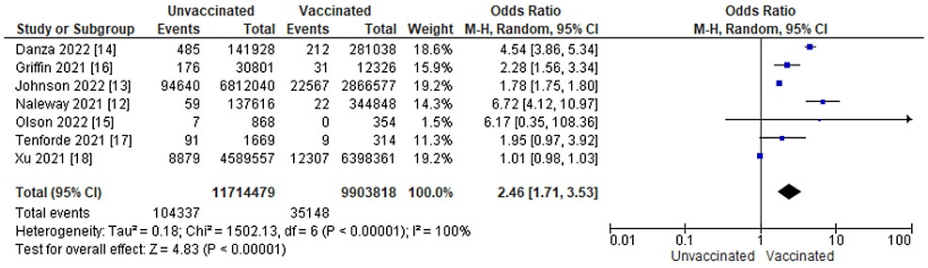

FIGURE 3: Mortality from COVID-19 infection by vaccination status

The figure displays for each study included in the meta-analysis a summary of statistics (number of events and sample size) for the unvaccinated and vaccinated groups, the Odds Ratio (OR) and its 95% Confidence Interval (CI), heterogeneity, and test for overall effect for the dichotomous outcome mortality from COVID-19 Infection [12-18].

GRADE Summary of Findings

Evidence for mortality from COVID-19 infection by vaccination status was available from seven observational studies included a total of 21,618,297 patients (Figure 4). After rating down one level for study design, we considered the evidence to be low-quality for an observational study design. These observational studies suggest that COVID-19 vaccination may substantially reduce mortality (OR 2.46, 95% CI 1.71 to 3.53; low-quality evidence) (Figure 3).

Outcomes	Number of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				The risk with COVID-19 vaccinated patients	The risk difference with COVID-19 unvaccinated patients
Mortality	21,618,297 (7 observational studies) Follow-up: Median 4 months	⨁⨁◯◯ Low	**OR 2.46** (1.71 to 3.53)	4 per 1,000	**5 more per 1,000** (3 more to 9 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

FIGURE 4: GRADE summary of findings

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

Discussion

This study evaluated the effectiveness of COVID-19 vaccination on patients with COVID-19 infection in the United States. In this evaluation, several outcomes were analyzed among individuals within the age range of 12-95 years using the following study design types: retrospective cohort, cross-sectional, randomized control trial and case-control study. Analysis of these studies reveals that COVID-19 vaccination confers a certain level of protection against poor outcomes in COVID-19-infected individuals.

The pandemic COVID-19 has had a global impact on mortality and morbidity. Vaccination has been linked to a considerable decrease in the number of symptomatic COVID-19 infections in adults as well as improved protection against severe disease [19-21]. Patients who were fully vaccinated were less likely to develop critical illness and require intensive care and were thus discharged faster [22-25]. Inadequate immunity in unvaccinated patients, combined with the growing prevalence of the delta variation, resulted in greater illness and fatality rates [26,27]. As the severity of the disease worsens, mortality rises dramatically [15,16]. Comorbidity risk influences both illness progression and mortality [28,29]. In this study, vaccinated individuals had considerably reduced mortality than unvaccinated patients.

In line with the majority of the articles used for this meta-analysis study, we noted that unvaccinated patients infected with COVID-19 are 2.46 times more likely to die from the COVID-19 infection compared to those that are vaccinated but infected with the virus. Our study is also in support of previous studies such as Tenforde, where it was noted that among patients hospitalized with COVID-19, the outcomes of death or invasive mechanical ventilation were associated with a lower likelihood when fully or partially vaccinated [17]. Moreso, in tandem with the study of Xu et al., it was noted that in a cohort of 6.4 million COVID-19 vaccines and 4.6 million demographically similar unvaccinated persons, recipients of the Pfizer-BioNTech, Moderna, or Jensen vaccines had lower non-COVID-19 mortality risks compared to the unvaccinated comparison group [18]. They also noted that there is no increased risk for mortality among COVID-19 vaccine recipients and this finding reinforces the safety profile of currently approved COVID-19 vaccines in the United States.

The risk of mortality among patients with COVID-19 infection is influenced by their sociodemographic characteristics, with an increased risk observed among those who are unvaccinated. In a recent study that compared mortality, recovery rates, and disease severity between men and women using a random-effects meta-analysis [30], the analysis found that male patients have a higher risk of mortality and a lower chance of recovery compared to female patients. Additionally, male patients were more likely to present with a severe form of COVID-19. The male-to-female ratio for cases was 1:0.9 [29]. This study however showed that there was no striking difference between males and females regarding disease susceptibility. The study however showed that the course of COVID-19 is more severe in men, but the vaccine may improve the prognosis in men, as fully vaccinated patients had a significantly higher mean age than unvaccinated and under-vaccinated patients [30].

Men may be more susceptible to COVID-19 due to differences in innate immunity, steroid hormones, and sex chromosomal characteristics [30,31]. Females may be at an advantage due to increased TLR7 and CD4+ cell expression, which ensures better elimination of viruses [31]. Male patients infected with COVID-19 have a 61% greater likelihood of dying from the infection than their female counterparts [31]. Cytokine storms have been observed as more frequently occurring in men, leading to multi-organ failure and death. Men had poorer rates of recovery and have longer viral RNA shedding for SARS-CoV-2, implying a slower recovery. Hormonal variables may also have an impact on disease phenotype and severity [28,32,33].

Age is a prognostic factor in determining the risk of mortality in patients with COVID-19 infections. This study included 486 patients with COVID-19, with 54.3% of them being unvaccinated. The median age was 53 years for unvaccinated and partially vaccinated patients and 62 years for fully vaccinated patients [28]. Critical illness was more prevalent in unvaccinated or partially vaccinated patients, and older age, higher disease severity, higher comorbidity index, and not being fully vaccinated were factors associated with higher mortality. The study highlights the importance of vaccination in reducing the severity of the disease and mortality, particularly in older patients with comorbidities [28].

It has been suggested that racial health disparities have contributed to an increased risk of mortality from COVID-19 infection. A systematic review and meta-analysis by Pal et al. showed that Native American men had the highest mortality risk [34]. Studies have also reported higher mortality rates among Black people, but this study found a similar risk of mortality among Black men compared to White men. These discrepancies between studies also may be due to different timing of sampling and trends in COVID-19 infection among different racial identity groups [35].

In contrast, another study examined the characteristics and outcomes of COVID-19 patients in California, Oregon, and Washington across different races/ethnicities [36]. The study found that Hispanic patients were disproportionately affected and had increased odds of hospital mortality. Other minority races/ethnicities were not significantly associated with increased mortality [36].

Limitations

There are several key limitations to our study that should be mentioned, such as the fact that the risks of COVID-19 infection are not the same for everyone, therefore the chance of exposure may influence the likelihood of COVID-19 vaccine acceptance and coverage. Finally, we were unable to independently assess the preventative impact of single doses against double and booster doses, as well as independently assess the effectiveness of the specific vaccines approved in the United States against distinct virus strains and clinical outcomes. Possible explanations include a lack of consistency in vaccine schedules and availability in the United States.

Conclusions

The meta-analysis study reviewed here provides evidence that COVID-19 vaccination confers a certain level of protection against poor outcomes in individuals infected with the virus. The study found that unvaccinated patients with COVID-19 are 2.46 times more likely to die from the infection compared to those that are vaccinated. Additionally, the study highlights the importance of vaccination in reducing the severity of the disease and mortality, particularly in older patients with comorbidities. Based on the findings of this study, it is recommended that individuals receive the COVID-19 vaccine as a means of protecting themselves against severe disease and mortality associated with COVID-19 infection.

Governments and health organizations should continue to encourage and facilitate vaccination efforts, particularly amongst high-risk populations such as the elderly and those with underlying health conditions. Efforts should also be made to address health disparities in access to and uptake of COVID-19 vaccines to ensure equitable distribution and protection for all populations. The study also emphasizes the need for data collection, improving access to testing, and the need for active intervention earlier in the disease course in addition to culturally appropriate public health messaging. The report also emphasizes the necessity of racial equity in vaccination distribution as well as the need for diversity in clinical trials to guarantee the safety and effectiveness of vaccines and therapies.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Exhibit I

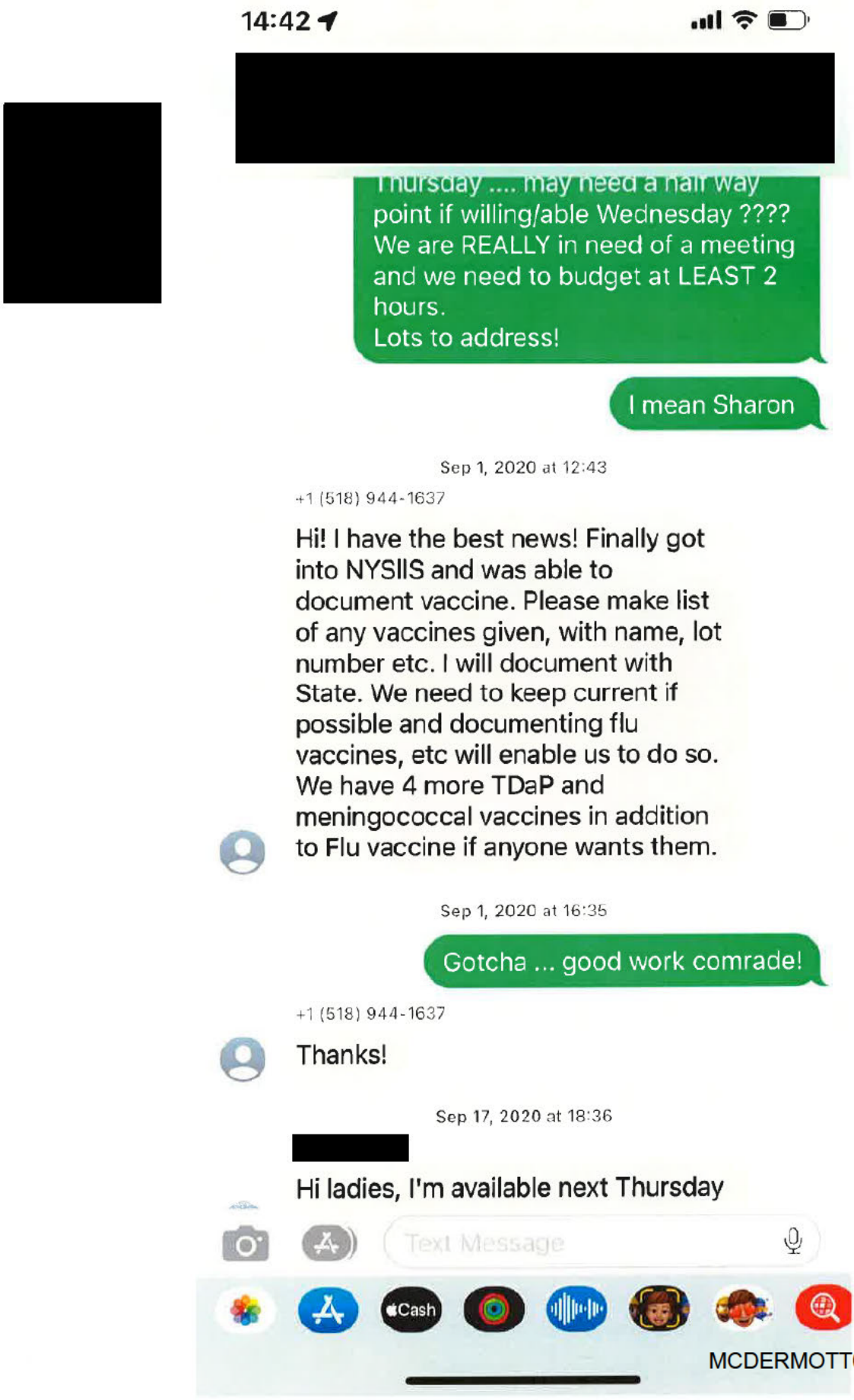

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Exhibit J

You are NOT REQUIRED to answer any questions of ANY law enforcement agency including the FBI. You ALWAYS have the right to consult with an attorney and you ALWAYS have the right to remain silent.

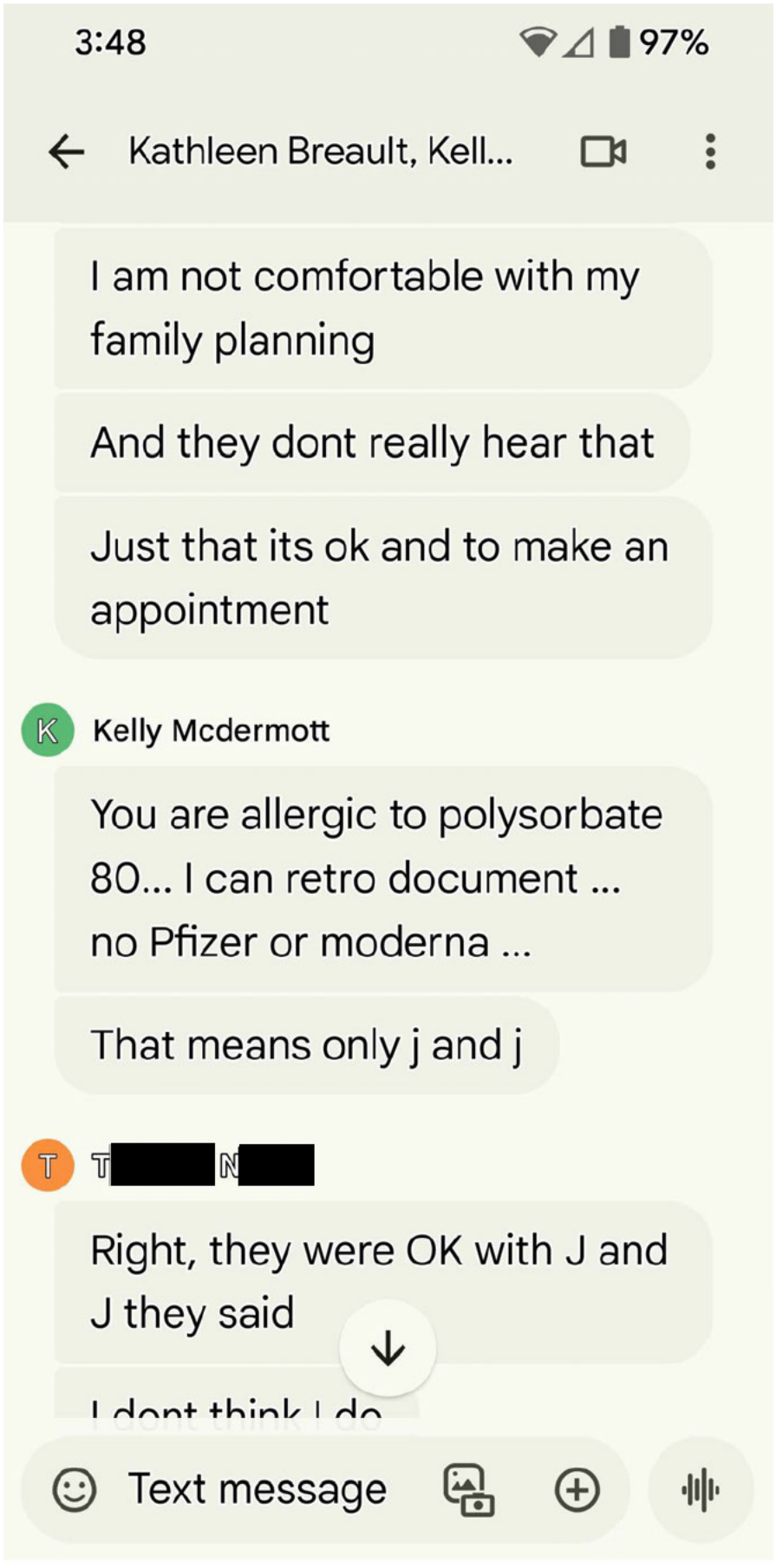
Understanding Your Right to Remain Silent and Your Right to Request the Advice of Counsel
Knowing the law can protect you. What follows is a basic understanding of your Constitutional rights.
First And Foremost, You Do NOT Have To Talk To ANYONE In Law Enforcement Including The FBI
There is no law enforcement organization in Colorado or anywhere in the country state or federal, including the FBI, that has the authority to compel you to answer their questions.

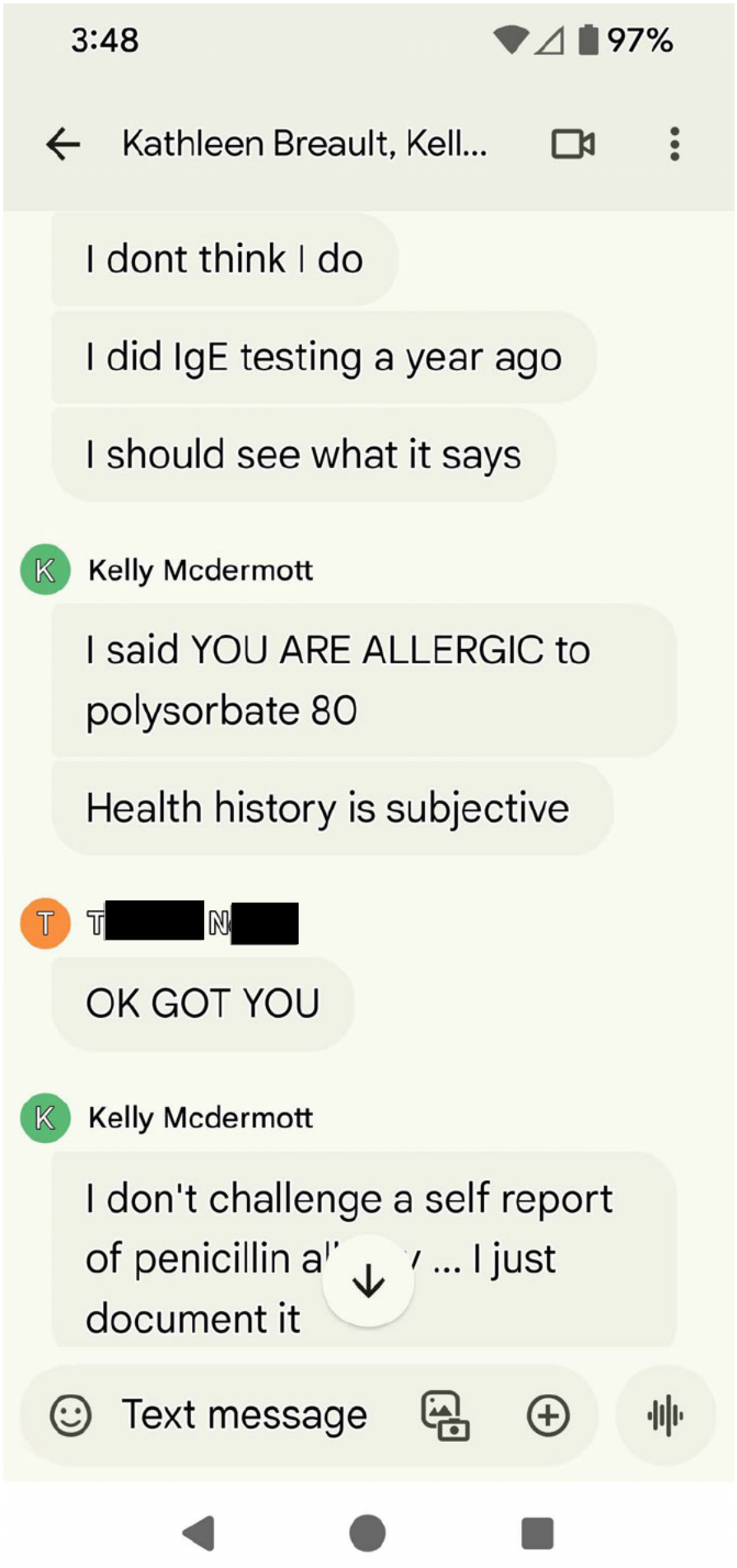
"The Fifth"
The Fifth Amendment to the Constitution provides that every person has the right to remain silent in the face of questions posed by any police officer or any governmental agent.

Here is the text of the Fifth Amendment:
Amendment V
No person shall be held to answer for a capital, or otherwise infamous crime, unless on a presentment or indictment of a grand jury, except in cases arising in the land or naval forces, or in the militia, when in actual service in time of war or public danger; nor shall any person be subject for the same offense to be twice put in jeopardy of life or limb; nor shall be compelled in any criminal case to be a witness against himself, nor be deprived of life, liberty, or property, without due process of law; nor shall private property be taken for public use, without just compensation.

IT IS A FEDERAL OFFENSE TO LIE!

Exhibit K


3:48
97%
Kathleen Breault, Kell...
I am not comfortable with my family planning
And they dont really hear that
Just that its ok and to make an appointment
K
Kelly Mcdermott
You are allergic to polysorbate 80... I can retro document ... no Pfizer or moderna ...
That means only j and j
T
T[redacted]N[redacted]
Right, they were OK with J and J they said
Text message


3:48
97%
Kathleen Breault, Kell...
I dont think I do
I did IgE testing a year ago
I should see what it says
K
Kelly Mcdermott
I said YOU ARE ALLERGIC to polysorbate 80
Health history is subjective
T
T[redacted]N[redacted]
OK GOT YOU
K
Kelly Mcdermott
I don't challenge a self report of penicillin a[redacted] ... I just document it
Text message